1965

Use of exercise tests in the diagnosis of incipient coronary artery disease

Kenneth Donald Hirsch
University of Nebraska Medical Center

USE OF EXERCISE TESTS IN THE DIAGNOSIS OF INCIPIENT CORONARY ARTERY DISEASE

Kenneth Donald Hirsch

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1965

Omaha, Nebraska

TABLE OF CONTENTS

The diagnosis of coronary artery disease is one which has assumed considerable importance in the practice of medicine today. As early as 1939 studies revealed that heart disease has been the leading cause of death in the United States since 1912.[18] In 1936, 48,622 deaths were ascribed to this cause and in 1937 it was responsible for 13.9% of all deaths.[18] More recent figures reveal that in 1962 in the United States alone there were approximately 700,000 deaths due to heart disease.[13] It has been estimated that of these, approximately 600,000 were due to acute myocardial infarction.[13] While the mortality rate of acute myocardial infarction varies, depending upon the type of patient population sampled as well as the severity and extent of the infarction, the over-all mortality of all acute coronary episodes is about 10%.[18] From these figures it becomes apparent that approximately six million acute coronary episodes occur annually in the United States.[13, 18]

In considering the diagnosis of coronary artery disease, it is not always the classical picture of angina pectoris which is encountered. It is not uncommon for a supposedly "healthy" individual to be told by his draft board, his plant physician, or his insurance agent that they are in fact "sick". A routine electro-

cardiogram on a completely asymptomatic person will often reveal significant abnormalities.[13] In the light of this knowledge, it is not too surprising to learn that at least one-third of all acute coronary occlusions occur in previously asymptomatic persons.[4,6,13,25] Since the acute attack represents only the end stages in a chronic progressive disease, and since it has been estimated that six million such attacks occur annually in the United States, then it becomes apparent that two million Americans are stricken yearly without prior warning after harboring "silent" coronary artery disease for varying lengths of time.[13]

While the figures presented above are alarming, they are verified in the reports of medical examiners and pathologists throughout the country. Their reports reveal a vast incidence of coronary artery disease at postmortem examination. Even in young persons dying of noncardiac causes, the entire spectrum of coronary atherosclerosis is seen, ranging from simple plaque formation to complete occlusion with transmural myocardial infarction.[13,18] In the middle-aged population at autopsy, 40% have anatomic evidence of unsuspected or "silent" myocardial infarction.[13,18] From these figures, it has been estimated that four to six per cent of the population over the age of 35 years has "silent" coronary artery disease.[13,18] In 1962 in the United

States the population in this age group was more than 79 million persons [13] making the number of persons with "silent" coronary artery disease in the range of three to four million rather than the two million persons previously calculated.[13,18]

The above figures and estimations begin to acquire meaning when you consider the importance which recognition of asymptomatic but significant coronary artery disease assumes. In these persons many measures can be utilized to prolong life. Thus it becomes necessary in some cases to eliminate or control factors such as severe exercises, anxiety, and other stressful situations which are known to be associated with a higher incidence of myocardial infarction. Weight reduction programs and other dietary measures may also be initiated, and in some cases, especially where a persons job involves the public safety, a job change may be necessary. An especially dangerous situation in such persons is the operating room, where an increased incidence of hypotension, shock, and death is seen before, during, or after the surgery.[13] This hazard is multiplied if in the course of silent coronary artery disease a "silent" infarction has occurred. If the presence of the disease is known in advance, special precautions and careful management during the

procedure results in morbidity and mortality in elective operations which approaches that of noncardiac patients.[13]

In recognizing the problem which exists, the next problem is to diagnose the coronary artery disease in such patients. The diagnosis of angina pectoris is a fairly straightforward procedure which can be made from the history alone in the majority of patients.[9,23] There remains, however, a large group of patients with chest pain which even the most skilled and conscientious physicians find difficult to classify.[14,23] Notable conditions which may mimic the "classical" anginal syndrome include spondylitis, arthritis, neuritis, fibrositis or myositis, peptic ulcer, cholecystitis, chronic pulmonary disease and neurocirculatory asthenia, just to mention a few.[14] There also remains the large group of people who are completely asymptomatic, adding to the problem.

One approach has been to do a careful history, physical examination, chest film, and biochemical survey on each person. One worker has reported 86% accuracy in differentiating between cardiac and noncardiac chest pain by history alone.[9] Other workers feel, however, that while the above measures may be helpful in some cases, they are often normal, even in advanced coronary artery disease.[14,23]

The electrocardiogram is probably the most promising tool in the diagnosis of coronary artery disease. It is generally felt, however, that the resting electrocardiogram is a notoriously insensitive measure of myocardial ischemia, even in the presence of "classical" anginal pain.[27] Wood [27] and Master [16] report that 50 to 70% of patients with "true" angina have completely normal resting electrocardiograms. It becomes apparent, then, that there is need for an objective standardized electrocardiographic test other than one taken at basal conditions to rule in or out coronary artery disease with reasonable certainty.

As early as 1931, Wood and others [26] compared the electrocardiographic response of normal subjects and those with angina pectoris to stair climbing. Thus began almost continuous research in the field of exercise testing up to the present day. By far the most widely used procedure is the "two-step test" introduced by Master and Jaffe in 1941. The test was evolved in order to provide a "standardized", safe, exercise test which forced the subject to an adequate yet reasonable level of exercise, sufficient to produce diagnostic electrocardiographic changes.[15] The test must be standardized for several reasons. First, severe exercise may induce

"ischemic" changes in healthy young persons.[11,15] Secondly, as indicated above, unless the exercise is sufficiently severe, the characteristic electrocardiographic changes may not be produced.[23] Finally, standardization is desirable for comparison with later tests as well as correlation with others of the same sex and age.[15,23]

The procedure for the Master two-step test requires that a two-step apparatus with two 9 inch steps be used. The apparatus should be from 18 to 22 inches wide. The subject should have eaten only lightly at his last meal. He must also be questioned and examined just prior to the testing to rule out acute illness or impending infarction. In addition, a resting electrocardiogram taken just prior to exercise should be normal. The procedure to be followed is carefully explained to the patient with emphasis placed on the instructions to cease exercising immediately at the first sign of chest pain or serious discomfort.[15]

In the actual testing, the subject ascends to the top of the two-steps and descends the other side--this counts as one "trip". He then turns toward the examiner and continues with the next "trip". By always turning toward the examiner, he continually reverses his direction of turn, thus eliminating dizziness. The process of

turning also provides a short rest so that the exertion is not as severe as if the total number of steps were traversed consecutively. The number of "trips" varies with the patients weight, age, and whether the test is a single (1½ min.) or double (3 min.) two-step test. Tables giving the recommended number of trips are standardized and stated in numerous articles.[15,16] Immediately after completing the test, the subject lies down and a tracing is recorded. Tracings are again recorded at two minutes and finally at six minutes after exercise. Leads V4, V5, V6, and II are the most helpful and are recorded in that order.[15]

The major criteria in the interpretation of the Master test are as follows:

1. Ischemic RS-T segment depressions of 0.5 mm or more are indicative of coronary disease until proven otherwise;

2. A completely negative double two-step (3 min.) test practically excludes ischemic heart disease; and

3. A "j" or junctional, depression of 0.5 mm or more may be classified as "functional" if the QX/QT ratio is less than 50% and the QTr is less than 1.08, but, conversely, any "j" depression with a QX/QT of 50% or greater, and a QTr of 1.08 or more is "organic". [12]

(See Figure 1).

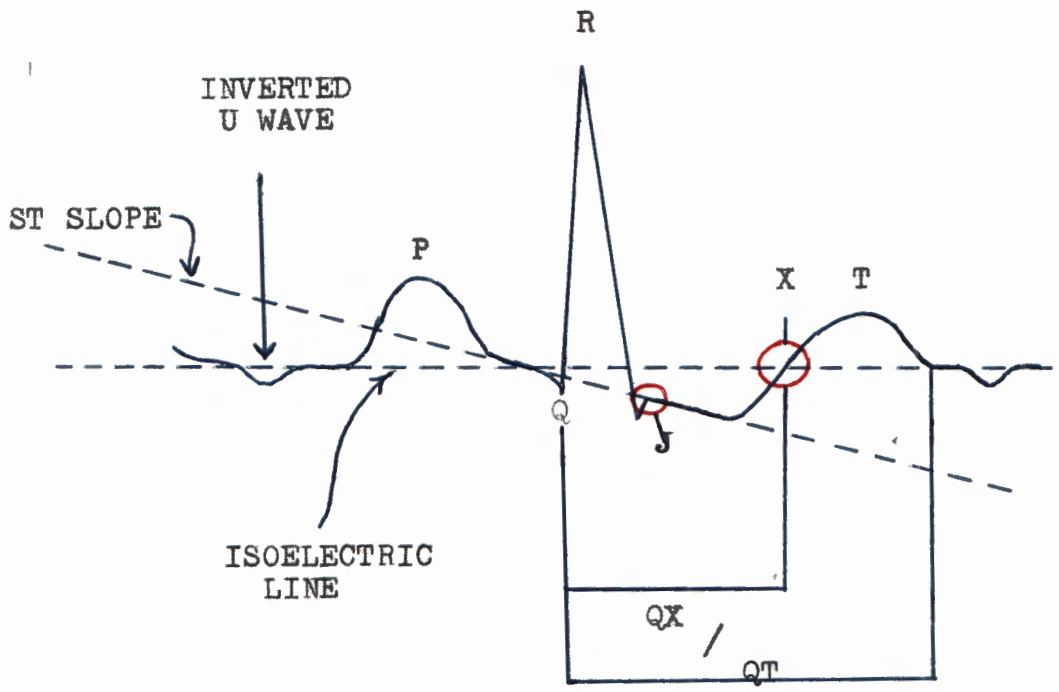

FIGURE I

An idealized abnormal electrocardiographic response to exercise, illustrating Master's criteria. The ST slope is downward, the QX/QT ratio is increased (greater than 0.5), and the U wave is inverted. (The QT ratio = QT/QTc, where QTc = $.40\sqrt{\text{R-R interval, sec.}}$) [23]

Master also interprets an inverted U wave as a positive two-step test.[15] A definitely inverted T wave is suspicious and should be considered as evidence of some abnormality, though not to the same extent as is ischemic RS-T depression, increased QX/QT fraction, or a prolonged QT ratio.[15] The sudden appearance of premature beats (especially if multifocal) immediately after exercise while the heart rate is still elevated, episodes of paroxysmal tachycardia, and paroxysmal flutter should be considered with caution.[15] Ventricular tachycardia, no matter how brief, is definitely abnormal.[15] Developments which are considered suspicious include BBB, interventricular block, and first, second, and third degree heart block.[15]

Application of the above data by Master in a series of 800 cases was done in 1964.[15] Of the 800 cases, 272 or 34% (227 men and 45 women) were diagnosed as having ischemic heart disease ("organic group"), while 528 or 66% were assigned to the "functional" group (444 men and 84 Women).[15] In the above series, Master reports a false-negative incidence of 3% (ie negative responses in patients thought to have ischemic heart disease).[15] In the same series, Master notes that

3.8% of the "functional" cases had a "positive" two-step test.[15] This degree of accuracy in detecting or excluding ischemic heart disease has been consistently reported by Master over the last twenty years[17,19] despite several revisions in his criteria over this same time period.

There has not been general agreement concerning tests based on the electrocardiographic response to exercise. Many investigators are critical of Master's results and question the tests validity, criteria, interpretation, and diagnostic reliability.[3,9,10,19,21,23,24] Some of these criticisms will be presented below.

In 1958 Lepeschkin reported a study involving 243 volunteer University of Vermont summer session students. All students were young and free of complaints attributable to coronary artery disease. In addition, all their physical examinations and resting electrocardiogram's were within normal limits. After subjecting all students to a double Master two-step procedure, three to six per cent of this predominately male population demonstrated a "false positive" electrocardiographic response.[10] In a mixed population, the figure rose to from 16 to 25%.[10,24]

In 1962, a double-blind study by Friedberg was conducted, attempting to evaluate the two-step's

accuracy in differentiating between anginal and non-cardiac chest pain. In this study 100 consecutive patients seen specifically for complaints of chest pain performed a double two-step test unless chest pain or other symptoms dictated earlier cessation of the testing. The test results were interpreted independently by two or three physicians and were classified according to various criteria which supposedly indicate a "positive" test. Table I gives the results of this study, but in summary, using the original criteria of Master (ie ST depression of 0.5 mm or greater), 39% of the nonanginal patients had a "false" positive result and 12% of the anginal patients had a "false" negative result. Making the criteria more liberal (ST depression of 2mm) reduced the "false" positive results to zero but increased the "false" negative rate to 82%.[9] Almost identical results were obtained by Mason in his study conducted in 1959.[19]

From this data Friedberg concluded that, "The new (1961) criteria of Master and Rosenfeld were not more satisfactory than the previous criteria recommended."[9] In fact, Friedberg questioned whether the electrocardiographic exercise tests were even necessary since he reported that an "unequivocal" diagnosis was made in 86% of the patients independently by at least two observers (in differentiating between anginal and noncardiac pain).[9]

TABLE I

Findings with Various Criteria for Positivity

Criteria: RS-T depression	Nonanginal Pain		Angina Pectoris	
	True Negative (%)	False Positive (%)	True Positive (%)	False Negative (%)
½mm. or more	61	39	88	12
3/4mm. or more	79	21	73	27
1mm. or more	92	8	57	43
1½mm. or more	95	5	30	70
2mm. or more	100	0	18	82
Master's new (1961) criteria*	68	32	82	18
Any ischemic Type or "j" Type of 1mm or more	74	26	67	33
Abnormal QT ratio (1.08 or more) as sole positive criterion	58	42	73	27

*(1) Any ischemic depression, or (2) "J" depression of 2mm. or more or (3) "J" depression under 2mm. with positive QX/QT fraction or positive QT ratio.[9]

Concerning the "J" junction depressions which Master feels are often significant [12,15], there is disagreement on this subject as well. Robb states in an article published in 1964 that "J" junction depressions are benign and in fact have an even better prognosis than no junctional depression.[21] Morever, "J" depressions of more than 3mm. have been observed during moderately severe exercise in healthy young persons.[23] Freidberg in his double blind study concurs after noting 26% false positives and 33% false negatives when applying the criteria of "J" junction depression of 1mm. or more to the postexercise electrocardiogram.[9]

Despite the frequent criticism of the two-step test, most authors do agree that it is a valuable aid in the diagnosis of coronary artery disease. Robb and Marks [21] state very definitely that ischemic S-T segment depression of any amount in the postexercise electrocardiogram is valid evidence of coronary insufficiency, due usually to atherosclerosis.[21] They further report that the degree of S-T segment deprssion is, "Directly related to the severity of impairment of the coronary blood flow."[21] Friedberg is more conservative and states that while S-T segment

depression of at least 1mm. usually confirms the presence of coronary artery disease, this degree of depression is, "Often absent in unequivocal cases of angina pectoris and conversely may be occasionally present in patients with nonanginal pain."[9]

In using results of the exercise tests to determine prognosis, Robb states that the absence of any post-exercise S-T segment depression, "Excludes the presence of latent coronary artery disease of moderate or advanced degree and wide extent."[21] Master concludes that a two-step test negative by his criteria provides strong evidence that the patient is free of heart disease.[15] On the other hand, the incidence of myocardial infarction was three times greater in persons with post-exercise ischemic electrocardiographic changes and the death rate was doubled.[3] Robb reinforces these findings by reporting that in 629 subjects with a normal electrocardiographic response to exercise, only 5 (.8%) subsequently had coronary deaths.[21] The group with ischemic postexercise changes in the electrocardiograph, however, had five times the likelihood of coronary death.[21] Franco[7], reporting the results of the medical department's records in a large industry, notes that in a series of 408 employees who had negative postexercise electro-

cardiograms, only 6 (1.5%) subsequently developed heart disease.

A recent publication has opened another area of controversy in the much used yet much critized exercise tests. Sheffield and Reeves correctly point out that in the final analysis, what is being tested in the exercise tests is the adequacy of coronary blood flow.[23] On this basis, an exercise test should be standardized and graded according to the challenge given to the coronary circulation by varying the coronary blood flow.[11,23] In the two-step test, however, the assumption is made that the coronary work parallels the work being done by the entire body. This assumption is made by specifying the number of "trips" to be made for each age group. Since there is considerable variation in the efficiency with which the heart accomplishes increased output during exercise, however, it is incorrect to assume that standardizing the number of "trips" a person makes will standardize the challenge given to the coronary circulation during the exercise.[23]

In health, the coronary blood flow varies in proportion to variations in the oxygen requirements of the myocardium. Thus an exercise test should be graded according to the changes induced in the requirement of

the heart muscle for oxygen.[23] According to the Laplace relationship of pressure, cardiac diameter, and tension, it follows that since the time integral of tension per heart beat is relatively constant during exercise, the myocardial oxygen consumption per minute would tend to vary in proportion to the heart rate.[23] Thus it seems reasonable to equate the challenge to the coronary circulation with the heart rate during exercise.[23]

In a new technique developed by Sheffield and Reeves called the graded exercise test (GXT), the preceeding theories are put to use. In this test, exercise is carried out at graded levels until the heart rate is 85% of the maximal predicted for the subject's age. At the first occurance of pain, "positive electrocardiographic changes," excessive dyspnea, or undue fatigue during the procedure, the test is terminated. Since the heart rate will vary according to the severity of the exercise, this test in essence has a self-adjusting end point, varying with the patients age and physical fittness.[23]

The GXT is conducted utilizing an ordinary direct-writing electrocardiograph with the precordial electrode at the V4 or V5 position. If care is taken to apply the electrodes properly and ground the machine, rate and rhythm analysis during exercise are satisfactory.

Using a single 12 inch step, the subject then runs up and down the step, alternately placing first one foot and then the other on the step while being watched closely for angina and electrocardiographic changes. In this preliminary test, the patient is allowed to select his own rate of exercise. Subsequent tests are then run, adjusting the exercise according to the response of the heart rate in the first test.

Short electrocardiographic tracings are made every 30 seconds during the exercise test and stylus motion is monitored continuously if a monitoring oscilloscope is not used. Upon attaining the specified end point, exercise is stopped and leads V4, V5, V6, I, II, and a VF are recorded in the recumbent position. Tracings are repeated at two, four, and six minutes after exercise. Another "level" of exercise is done after the heart rate returns to the control level, usually in six to thirty minutes. In most cases, only two "levels" of exercise are done, but occasionally three are required.[23]

To evaluate the new test, a group of 98 "normal" subjects aged 14 to 94 years and 83 patients with probable angina pectoris were selected. Single and double Master two-step tests as well as a GXT pro-

cedure were done on each person. It was noted that the Master tests produced widely varying degrees of tachycardia and were "positive" in only 57% of the patients with clinical angina.[23] By comparison the GXT test produced age-standardized degrees of tachycardia and required varying amounts of exercise to attain these heart rates. Using the criteria of 1mm. ST segment depression, 76% of the patients with clinical angina had "positive" postexercise electrocardiographic changes using the GXT test.[23] An interesting observation in reviewing these results was that nearly half (46%) of all "positive" electrocardiographic changes were seen when the heart rate was at least 90% of the maximum predicted rate for each age. In this series, the Master test produced heart rates which averaged about 75% of the maximum predicted rate, although this figure varied widely. It is to be expected, then, that the Master test results in a significant number of "false negatives" which could be avoided by using the GXT.[23]

Another relatively new innovation in the field of exercise testing should be mentioned because of the potential which it possesses. This is of course the use of telemetering devices to transmit and record the electrocardiographic record while the exercise is

actually occuring. Advantages of being able to monitor athletes, astronauts, and even businessmen during the stressful situations which they encounter daily need hardly be mentioned. In exercise testing, a transmitted pattern during the actual stress would probably be of more value than the postexercise recording in detecting coronary artery disease.[2,8] There is also the advantage of immediate recognition of ischemic changes before actual myocardial damage has occurred.[21] One author reported the case of a young man who developed ventricular tachycardia and arrhythmia during a telemetered exercise test. Immediate recognition enabled prompt cessation of the testing and possible disaster was averted.[5]

One objection to radiotelemetering devices is that they are expensive to buy and maintain and the electrocardiographic patterns obtained may be difficult to interpret because of artifacts which they may contain. Technical work and development in this area have been done by Dunn at the University of Nebraska, however, and the transmitted patterns appear to be of good quality and are free of artifacts.[5] Regarding interpretation of telemetered electrocardiograms, the major difficulty is in deciding which criteria to apply.

The criteria used in postexercise patterns may not apply because different leads are used, faster heart rates are obtained, and the tracing is taken in the upright rather than the recumbent position. In addition, muscle contractions and movement may alter the telemetered electrocardiographic patterns.[12,22] Despite these difficulties, however, radiotelemetry represents a variation of electrocardiography which has much potential and possible future application. Further study and statistical analysis must be done, however, before this potential can be realized.

DISCUSSION

The figures presented at the beginning of this paper regarding the magnitude of coronary artery disease require little comment. The asymptomatic or "silent" counterpart is a diagnostic problem of importance to both the patient and the physician since dietary control, restrictive measures regarding stress situations, and careful medical and surgical management may be necessary.

Evidence presented in this paper affirm that probably the most valuable tool in the diagnosis of coronary artery disease is the electrocardiographic response to exercise. Master has been without a doubt the most ardent worker in this field. His criteria, however, in a state of continual flux, have become more and more complex and difficult to apply, despite the fact that he has consistently reported excellent results using them. Several questions arise concerning these results. The first is whether a 0.5mm depression is that easily detected and reproduced at high heart rates and with the tachypnea which must accompany exercise. The second is whether in his desire to explain away apparent "false" positive and negative tests he may not allow the clinical picture to bias his

"objective" criteria in the borderline cases which certainly must occur.

Regarding the criticisms leveled at the Master test, a frequent argument is a large percentage of "false" positive and negative results. In the final analysis, however, it is difficult to assert that any given electrocardiographic response is indeed "true" or "false" in the absence of documented (eg angiography; autopsy; etc.) proof that coronary artery disease does or does not exist. Despite all criticism, however, it is generally agreed that ischemic ST segment depression is evidence of coronary artery disease while no ST segment depression rules out at least moderate to advanced coronary artery disease.

Concerning the graded exercise test, the physiological principles equating the challenge to coronary circulation to the heart rate are certainly reasonable. Also reasonable is the criticism that the Master test fails in most cases to standardize the challenge to the coronary circulation because of the variable heart rates obtained in the prescribed number of "trips." This graded exercise test certainly has potential, but at the present state of development has had insufficient use and statistical analysis to form any valid conclusions.

CONCLUSIONS

1. Six million Americans each year have acute coronary episodes. One-third of these occur in asymptomatic persons and pose a diagnostic problem of importance to both the patient and the physician.

2. The electrocardiographic response to exercise remains the most useful tool in the diagnosis and prognosis of coronary artery disease, despite limitations in interpretation.

3. Ischemic S-T segment depression in any amount is evidence of coronary artery disease; the amount of depression correlates with the severity and extent of the coronary artery disease.

4. Absence of any S-T segment depression excludes coronary artery disease of moderate or advanced degree.

5. "J" junctional depression is a controversial issue but is probably not abnormal unless there is a flat or downsloping ST segment.

6. The Master test does not standardize the challenge to the coronary circulation whereas the graded exercise test promises to do so, eliminating some avoidable false negative results.

7. Radiotelemetry represents a variation of electrocardiography having much future potential but requiring further study and statistical analysis before valid conclusions may be drawn.

BIBLIOGRAPHY

1. Bazett, H. C.: Analysis of Time-Relations of Electrocardiograms, Heart 7: 353-370 (Aug 27) 1920.

2. Bellet, S. et al: Radioelectrocardiography During Exercise in Patients with Anginal Syndrome: Use of Multiple Leads, Circulation 29: 366-375 (March) 1964.

3. Dimond, G. E.: The Exercise Test and the Prognosis of Coronary Heart Disease, Circulation 24: 736, 1961.

4. Doscher, N. and Poindexter, C. A.: Myocardial Infarction Without Anticoagulation Therapy: Deaths, Emboli, and Analysis of Factors Influencing Mortality, Amer J Med 8: 623-633 (May) 1950.

5. Dunn, F. L. and Beenken, H. G.: Short Distance Radio Telemetering of Physiological Information, JAMA 169: 1618-1621 (April 4) 1959.

6. Evans, W. and Lloyd-Thomas, H. G.: Infrequent Normal Electrocardiogram in Cardiac Pain, Amer Heart J 62: 51-64 (July) 1961.

7. Franco, S. C. et al: Periodic Health Examinations: Long Term Study, 1949-1959, J Occup Med 3: 13-20 (Jan) 1961.

8. Freiman, A. H. et al: Electrocardiogram During Exercise, Amer J Cardiol 5: 506-515 (April) 1960.

9. Friedberg, C. K. et al: The Two-Step Exercise Electrocardiogram; A Double-Blind Evaluation of its Use in the Diagnosis of Angina Pectoris, Circulation 26: 1254, 1962.

10. Lepeschkin, E. and Surawicz, B.: Characteristics of True-Positive and False-Positive Results of Electrocardiographic Master Two-Step Exercise Tests, New England J Med 258: 511, 1958.

11. Lloyd-Thomas, H. G.: Exercise Electrocardiogram in Patients with Cardiac Pain, Brit Heart J 23: 561, 1961.

12. Master, A. M. and Rosenfeld, I.: Monitored and Post-Exercise Two-Step Test, JAMA 190: 494-500 (Nov 9) 1964.

13. _____: "Silent" Coronary Artery Disease, Med Trib 5: 15 (April 29) 1964.

14. _____: Spectrum of Anginal and Noncardiac Chest Pain, JAMA 187: 894-899 (March 21) 1964.

15. _____: Criteria for Clinical Application of "Two-Step" Exercise Test: Obviation of False-Negative and False-Positive Responses, JAMA 178: 283-289 (Oct 21) 1961.

16. _____: "Two-Step" Exercise Test Brought up to Date, New York J Med 61: 1850-1857 (June 1) 1961.

17. _____ et al: Master Two-Step Exercise Electrocardiogram: Exclusion of the "False-Positive", Abstract, Circulation 20: 737, 1959.

18. _____ et al: Prevalence of Coronary Artery Occlusion, New York J Med 39: 1937-1940 (Oct 15) 1939.

19. Mason, R. E.: The Master Test in Patients with Coronary Heart Disease and in Normal Subjects, The Heart Bulletin 8: 67, 1959.

20. Mattingly, T. W.: Post-Exercise Electrocardiogram: Its Value in Diagnosis and Prognosis of Coronary Artery Disease, Amer J Cardiol 5: 395-409 (March) 1962.

21. Robb, G. P. and Marks, H. H.: Latent Coronary Artery Disease: Determination of Its Presence and Severity by Exercise Electrocardiogram, Amer J Cardiol 13: 603-618 (May) 1964.

22. Rosenfeld, I. et al: Recording Electrocardiogram During Performance of Master Two-Step Test: Part I, Circulation 29: 204-211 (Feb) 1964.

23. Sheffield, L. T. and Reeves, T. J.: Graded Exercise in the Diagnosis of Angina Pectoris, Modern Concepts of Cardiovascular Disease 34: 1-6 (Jan) 1965.

24. Simonson, E. and Keys, A.: Electrocardiographic Exercise Test: Changes in Scalar ECG and in Mean QRS and T Vectors in Two Types of Exercise, Amer Heart J 52: 83-105, 1956.

25. Smith, G. B. Jr. and Lamb, L. E.: Electrocardiographic Findings in 67, 375 Asymptomatic Subjects, Amer J Cardiol 6: 190-199 (July) 1960.

26. Wood, F. C. et al: Angina Pectoris, Arch Intern Med 47: 339, 1931.

27. Wood, P. et al: Effort Test in Angina Pectoris, Brit Heart J 12: 363-371 (Oct) 1950.