The Exercise Test in Diabetic Patients as Studied by Radioelectrocardiography

By Samuel Bellet, M.D., and Laurian Roman, M.D.

SUMMARY
Pathological, clinical, and epidemiological studies have shown that in diabetic subjects, the incidence of coronary heart disease is higher than in a nondiabetic population. In a group of 85 diabetic subjects free of clinical evidence of heart disease and exhibiting no significant abnormality in the resting electrocardiogram, an exercise electrocardiographic test was performed. In 22.3% results of the exercise test were positive; in similar studies of nondiabetic subjects, using the same technique and criteria, the incidence of positive electrocardiographic exercise tests ranged from 8 to 12%. Since a positive exercise test is usually associated with latent coronary artery disease, such findings would be considered of importance in the diagnosis and for following the evolution of this disease. It is suggested that the exercise test be performed routinely in diabetic subjects. By this means, coronary heart disease may be detected in the asymptomatic stage; this is particularly important for diabetic subjects, in whom even advanced coronary heart disease may be clinically silent.

Additional Indexing Words: ECG exercise test

A LARGE NUMBER of pathological, clinical, and epidemiological studies1-22 have shown that the incidence of coronary heart disease is significantly increased among diabetic patients.

The purpose of this investigation was (1) to determine the presence of latent coronary heart disease in diabetic patients by the electrocardiographic exercise test; and (2) to compare the incidence of positive exercise tests in diabetic subjects and in a similar group of normal subjects.

Methods
The diabetic patients were from the Diabetic Clinic of the Philadelphia General Hospital. The diagnosis of diabetes was established in all cases by the usual criteria (either one or both of the following): persistent high values for fasting blood sugar or abnormal glucose tolerance test (fasting blood sugar > 110 mg% or 2-hour values > 120 mg% during the glucose tolerance test). The blood sugar was determined by the Somogy-Nelson method. Most of the patients had mild or moderately severe diabetes. In our clinic, the following criteria were employed*: Patients who required only diet or oral medication (sulfonamides), or both were considered to have mild diabetes; patients who, in addition to diet, required insulin, up to 40 units of NPH insulin per day, were considered to have moderately severe diabetes; patients with a tendency toward acidosis or who required larger doses of insulin for control of their diabetes, or both, were considered to have severe diabetes. By this classification, 50 of our patients had mild diabetes, 29 had moderately severe diabetes, and six had a severe grade of diabetes.

We included in our study only patients in whom diabetes had been diagnosed at least 2 years prior to this study; the known duration of

*Patients are usually classified as having mild, moderately severe, and severe grades of diabetes; however, the basis of such classification is wholly arbitrary and is quantitatively ill defined.
the diabetes in most cases ranged from 2 to 7 years.

In this study, we accepted diabetic subjects whose diabetes was uncomplicated by another illness. The following were excluded from this study: (1) subjects with clinical evidence of angina, myocardial infarction, or other types of cardiac abnormality; (2) those with electrocardiographic abnormalities except minor T-wave changes; (3) subjects with hypertension (systolic pressure over 150 mm Hg or diastolic pressure over 90 mm Hg, or both); and (4) those with significant anemia (hemoglobin < 10 g).

Eighty-five diabetic patients fulfilled these criteria. The method of study follows: After a 12-lead electrocardiogram was recorded in the supine position as a control, a double two-step test was then taken in which the electrocardiogram was recorded in the standing position by the technique of radioelectrocardiography.* Leads II, V₄ and V₆ were recorded before, continually during, and at periods of 1, 3, and 5 minutes following exercise. The technique, apparatus, type and placement of electrodes have been discussed in previous communications. The results of exercise test follow: ischemic type of ST-segment depression $\geq 1$ mm, or the appearance of multiple premature ventricular contractions, or both. Also, in every patient, fasting blood cholesterol was determined by the technique of Abell.

**Results**

The age and sex of our subjects are indicated in table 1. The results of the exercise

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*The instrumentation complies with the specifications of the American Heart Association. The Sanborn specifications (Viso 100 Recorder) state that the response ranges from 0.1 to 80 cycles per sec. The response of the RKG 100 is from 0.15 to about 1,000 cycles per sec. At various degrees of sensitivity, the curve of the Sanborn electrocardiogram alone and the combined Sanborn and the RKG system were almost identical. Comparison of the ECG taken simultaneously by the RKG and the standard Sanborn ECG before, during, and after exercise consistently shows no difference in the contours of the ECG.
test and the correlation of the exercise test with blood cholesterol values are given in tables 2 and 3. Figures 1, 2, and 3 show the characteristic electrocardiographic findings observed.

As can be seen in table 2, in 19 of the 85 subjects (22.3%), the electrocardiographic test was positive; this incidence is significantly higher than that observed in unselected normal subjects of relatively similar age groups. In these, positive exercise tests were obtained in only 8 to 12% of the cases.28

The most frequent finding on which the diagnosis of positive exercise test was made is an ischemic ST-segment depression; in 17 out of 19 subjects with positive electrocardiographic exercise tests, an ischemic ST depression occurred either alone or associated with other changes. Only in two cases was the exercise test considered positive in the absence of an ischemic ST-segment depression because of ventricular bigeminy occurring during exercise.

Table 2 shows that a high incidence of positive exercise tests was found in the 23 younger diabetics, under 40 years of age (17.4%).

Table 3 shows that the incidence of high blood cholesterol was significantly increased in the diabetic subjects; in 40.1% it exceeded the generally accepted upper normal limit of 260 mg%. However, among those with a positive exercise test, 69.3% had a blood cholesterol ≥ 260 mg%, whereas only 33.3% of those with a negative exercise test had a cholesterol value ≥ 260 mg%. In a previous publication we reported a correlation between increased values of blood cholesterol and an increased incidence of positive exercise tests in normal subjects.29

Discussion

The increased incidence of coronary disease among diabetic subjects has been well established in both clinical and necropsy studies.1-22 Pathological studies of large groups of patients have shown that coronary heart disease was twice as frequent in diabetic males and three times as frequent in diabetic females as in nondiabetic subjects.2 In other pathological studies, the incidence of myocardial infarction and coronary occlusion was also found to be two to three times more frequent in diabetic than in nondiabetic subjects.3-6 There is considerable evidence of premature aging of vessels. Premature atherosclerosis has been observed in 29 of 50 diabetic patients by Huston and Abboud.80 In addition, Herman and Gorlin81 observed that among subjects with premature coronary disease, a large number had clinical or preclinical diabetes. In a high percentage of 50 subjects with angina pectoris occurring before the age of 50 years and in whom advanced coronary artery disease was documented by selective coronary arteriography, the blood sugar or the glucose tolerance test was abnormal. These authors stressed the importance of diabetes mellitus, even mild and manifested only by a positive glucose tolerance test, as an important factor leading to the early development of coronary artery disease.

Clinical studies have also shown an increased incidence of coronary heart disease in diabetic subjects; about 50% of hospitalized diabetic subjects manifested clinical evidence of coronary heart disease.7-16 Moreover, the clinical course of coronary heart disease was apt to be more severe and the progression more rapid than in nondiabetic patients. Not only is the immediate mortality higher with myocardial infarction, but the mortality rate after 60 days and after 5 years is significantly higher in diabetic subjects.7,16

Although several epidemiological studies have revealed a significant correlation between diabetes mellitus and coronary heart disease,17-22 relatively little data are available with regard to the electrocardiographic exercise test in diabetic subjects. In the present study, the incidence of positive exercise tests was much higher (that is, 22.3%) in diabetic subjects who manifested no clinical evidence of heart disease or hypertension than in normal subjects studied by the same technique. In a series of 3,000 apparently normal subjects, aged 30 to 65 years, the incidence of positive exercise tests, studied with a similar
Patient is a man, aged 48 years, with mild diabetes. This patient was asymptomatic; clinical examination revealed the heart to be normal. The 12-lead electrocardiogram was within normal range. Radioelectrocardiogram (V6): Note the normal tracing in the lying position. In the

Figure 1
Figure 2

Lead V₅: Patient is an asymptomatic male, aged 53 years. The 12-lead electrocardiogram was normal. Note the normal tracing in the standing control. During exercise, note the ST-segment depressions at 60 sec, 120 sec, and 180 sec. Immediately after exercise (stat), note the ST-segment depression. At 1, 3, and 5 minutes, ischemic ST-segment depressions are observed. The tracings taken simultaneously with the Sanborn ECG are identical with those of the RKG.

Standing position, slight ST-segment depressions are noted. During exercise (at 120 sec), note marked ST-segment depression. In the postexercise period, ST-segment depressions are noted at 1 and 3 minutes; and an ischemic ST-segment depression is noted at 5 minutes.
Figure 3

Lead V₆: Patient is a male, age 48 years. Note the control tracing showing slight ST-segment depressions which are not particularly significant. The ST-segment depressions increase gradually during exercise. The stat tracing (immediately upon cessation of exercise) shows marked ST-segment depressions. In the postexercise period at 1, 3, and 5 minutes, significant ST-segment depressions may be observed. There is no significant change between the tracings recorded with the RKG and those simultaneously recorded by the Sanborn ECG machine.
technique, ranged from 8 to 12%. In one group consisting of 795 male subjects, an average follow-up of 3 years was available.\textsuperscript{28} Ninety-five (11.9%) had initial positive exercise tests, and 700 (88.1%) had negative tests. During the 3-year follow-up period, 13.7% of the subjects with positive tests later developed clinical coronary heart disease; whereas coronary episodes occurred in only 1.4% of those subjects with negative tests. These results illustrate the value of the electrocardiographic exercise test in delineating among asymptomatic subjects a high-risk group for the development of subsequent coronary heart disease and are in keeping with other large-scale clinical, epidemiological, and pathological studies\textsuperscript{32-38} which have shown that frequently a positive electrocardiographic exercise test accompanies or precedes the occurrence of clinically overt coronary heart disease. These facts have led us and others\textsuperscript{32-34, 39} to consider that in the absence of any other obvious cause which may impair the coronary circulation or the myocardial metabolism (congenital or rheumatic heart disease, hypertension, severe anemia, digitalis treatment), a positive electrocardiographic exercise test is generally considered to be due in most instances to coronary heart disease, overt or clinically silent. We are aware that there may be exceptions; however, we feel that in these circumstances the chances that the positive electrocardiographic exercise test is due to coronary heart disease are high. Studies performed by us\textsuperscript{29} and others\textsuperscript{49} in groups of subjects with no clinical or electrocardiographic evidence of overt coronary heart disease but in whom one or several coronary-risk factors were present (hypercholesterolemia, hypertension, heavy cigarette smoking) have shown that in such subjects the exercise test is frequently positive. The high incidence of positive exercise tests in such "coronary-prone" subjects is additional proof of the value of the electrocardiographic exercise test in the detection of latent coronary heart disease.

In this study, the criteria for positive findings, as we mentioned before, were ischemic type of ST-segment depression equal to or more than 1 mm or numerous multiple premature ventricular contractions induced by exercise. The significance of the ischemic ST-segment depression has been substantiated by many prospective studies.\textsuperscript{28, 30, 34, 36, 41} The significance of the occurrence of premature beats following moderate exertion is somewhat controversial. Some observers\textsuperscript{42-44} feel that they are of questionable significance; however, others\textsuperscript{45-47} feel that such changes constitute abnormal findings usually associated with coronary heart disease. Our laboratory has been particularly interested in the significance of premature beats produced by exercise for many years. In normal subjects, aged 17 to 25 years, studied during as well as after exercise, no ventricular premature beats induced by exercise were observed in a series of 500 subjects while the two-step test was performed. We have observed premature beats, and occasionally, paroxysms of tachycardia, in the age group of 50 years and above in whom coronary disease could not be ruled out. They were most frequently observed in patients with angina and coronary disease occurring usually with or immediately preceding the presence of ischemic ST-segment changes. That is why we, together with the above-mentioned authors,\textsuperscript{45-47} feel that exercise-induced premature ventricular contractions usually represent an abnormal finding.

In our present study only two subjects were considered to have positive exercise tests because of the occurrence of numerous premature ventricular contractions (in the form of ventricular bigeminy) induced by exercise; in the other 17 subjects, an ischemic type of ST-segment depression was present. Even if we would exclude these two subjects from the series, the incidence of positive tests in the diabetic patients would still be high, that is, 17 out of 85 (20%).

This study suggests that the exercise test is of particular value in detecting subjects with asymptomatic coronary artery disease. Increasing the amount of exercise may well lead to an increase in the sensitivity of the
method. Recently, it has been shown that a more strenuous type of exercise performed in middle-aged subjects either apparently normal, or with angina pectoris, increased the incidence of positive findings. We have also studied the electrocardiogram during and after a strenuous type of exercise in a coronary-prone group of middle-aged subjects (with diabetes, hypertension, or atypical chest pain, or all three). Compared to the double two-step test, this technique has increased the yield of ischemic electrocardiographic changes by 12%.49

In conclusion, we feel that the electrocardiographic exercise test may pinpoint clinically the earlier appearance of coronary heart disease. These tests are of added importance in diabetic subjects since considerable data indicate that coronary heart disease, including myocardial infarction, in the diabetic is often associated with less severe chest pain than in nondiabetic subjects and even with the absence of pain.12, 16, 50

It is significant that the incidence of positive exercise tests is much greater in those diabetic subjects with increased concentration of cholesterol in the blood. These findings are in keeping with the thesis that the progression of coronary heart disease is, in general, greater in subjects with hypercholesterolemia. Abnormalities of blood cholesterol or other blood lipids in diabetics have been reported previously.7, 61–58 It is possible that diabetes favors the earlier and more frequent occurrence of coronary heart disease because of these blood lipid abnormalities with which it is frequently associated.

These findings suggest that exercise tests should be performed more frequently in diabetic subjects to detect the pre-clinical state of coronary artery disease.

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References


Healthy Kidneys—Superb Servants

It is no exaggeration to say that the composition of the blood is determined not by what the mouth takes in but by what the kidneys keep: they are the master chemists of our internal environment, which, so to speak, they manufacture in reverse by working it over completely some fifteen times a day. When, among other duties, they excrete the ashes of our body fires, or remove from the blood the infinite variety of foreign substances that are constantly being absorbed from our indiscriminate gastrointestinal tracts, these excretory operations are incidental to the major task of keeping our internal environment in an ideal, balanced state. Our bones, muscles, glands, even our brains, are called upon to do only one kind of physiological work, but our kidneys are called upon to perform an innumerable variety of operations. Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival; but should the kidneys fail to manufacture the proper kind of blood neither bone, muscle, gland nor brain could carry on.—HOMER W. SMITH: From Fish to Philosopher. Boston, Little, Brown and Company, 1953, p. 4.
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SAMUEL BELLET and LAURIAN ROMAN

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