Exercise Testing with Myocardial Scintigraphy in Asymptomatic Diabetic Males


SUMMARY Sixteen diabetic males, 32–60 years old (mean 48.7 ± 8.9 years), without clinical or electrocardiographic evidence of heart disease and 12 normal volunteers, mean age 48.9 ± 8.8 years, participated in maximal exercise testing combined with thallium-201 myocardial scintigraphy. A motorized treadmill was used with the Bruce protocol. A standard 12-lead ECG and systolic blood pressures were recorded every minute during exercise and for at least 8 minutes in the postexercise period. Echocardiograms were obtained at rest for chamber dimensions and myocardial function.

At maximal stress the heart rate attained by the normal controls was higher (174.5 ± 17.4 beats/min) than that of the diabetic males (163.1 ± 9.9 beats/min) (p < 0.05). Although the maximal systolic blood pressure for both groups was comparable (215.9 ± 32.5 mm Hg for the diabetics vs 209.6 ± 21.6 mm Hg for the normal controls), maximal systolic blood pressures > 210 mm Hg occurred in only three of 12 normal subjects (25%) but was noted in nine of 16 diabetics (56.2%).

The duration of exercise was longer in controls (663.0 ± 92.1 seconds) than in the diabetics (519.0 ± 127.2 seconds) (p < 0.005). The estimated maximal oxygen consumption was also increased in controls vs diabetics (p < 0.005). Functional aerobic impairment was greater in the diabetics (10.4 ± 19.1%) compared with normal controls (−7.8 ± 9.0%). Significant ST-segment changes were present in two diabetics and one control subject. Of the 12 diabetic subjects who underwent exercise testing with thallium-201, five (41.7%) had abnormal perfusion during stress or with both stress and rest. Such abnormalities were present only once in the 11 perfusion studies in healthy subjects.

Echocardiographic findings were similar in both groups. However, the percent of myocardial fractional shortening was smaller in diabetics than in controls (p < 0.05). Of the 12 subjects who underwent myocardial scintigraphy, an abnormal exercise ECG or a myocardial perfusion defect appeared in seven (58.3%) of the diabetics without overt cardiac disease and in only one normal subject. This suggests that asymptomatic subjects in this high-risk category of middle-aged diabetic males should be under close and repeated surveillance.

CORONARY ARTERY DISEASE is the leading cause of death in diabetics.1,2 More than half the deaths in subjects whose diabetes began after the age of 20 years have been attributed to a coronary event.1,2 In those whose disease began after age 40 years, clinically significant coronary arteriosclerosis is frequent, especially in patients whose illness is of long duration.2 Diabetic females, moreover, are exposed to the same risk as the males.2 Pathologic changes in the coronary arteries may be extensive and may result in advanced myocardial dysfunction without overt myocardial infarction or angina pectoris.3 Diabetes mellitus may be a prime cause of ischemic cardiomyopathy.3 However, the assumption that disease of the large coronary arteries is the sole cause for the increased cardiac mortality has been challenged. Small-vessel disease has been implicated in the pathogenesis of myocardial dysfunction.4,5 In a recent report, intimal proliferation was observed in biopsy specimens from the hearts of eight diabetic patients with cardiac failure or angina.6 The Framingham group suggested that diabetes mellitus alone could result in myocardial disease, and that in diabetics the incidence of congestive heart failure could not be entirely accounted for by such established entities as hypertension or ischemia.7 Despite the controversy surrounding the relative importance of each of these factors in the pathogenesis of diabetic heart disease, it is evident that the process is far advanced before overt clinical manifestations appear. The purpose of this investigation was to establish a method for the early detection of latent cardiac disease in a group of diabetic patients. Stress testing in subjects without clinical evidence of cardiac pathology has been found to produce a high incidence of false-positive results.8–12 However, with the advent of radionuclide perfusion studies in conjunction with exercise testing, the sensitivity of this method has increased.13 Furthermore, evaluation of the physiologic responses to stress have also improved the diagnostic accuracy of such tests.14 We, therefore, studied a group of middle-aged diabetic males during maximal exertion on a motorized treadmill with radionuclide scintigraphy.

Material

Patient Selection

A regular survey of the hospital wards and medical and diabetic outpatient services of the New York Veterans Administration Hospital was made to
register diabetics who had no signs or symptoms of cardiac disease. Each candidate underwent physical examination after a personal interview and review of his medical record. Only diabetic patients with negative chest x-rays who were free of valvular disease, myocardial infarction, chest pain, dyspnea, palpitations or syncope were selected. Sixteen diabetic males were found who qualified for the study. All had normal ECGs except for one subject (case 7), who had an rSr' in V1 and a QRS duration of 0.14 second. None had sustained hypertension, although three (cases 8, 11 and 12) had transient blood pressure elevations. These 16 males ranged in age from 32–60 years (mean 48.7 ± 8.9 years). The duration of diabetes was from 2 months to 16 years (mean 7.8 ± 6.6 years) (table 1). Twelve age-matched normal male volunteers (34–65 years of age, mean 48.9 ± 8.8 years) and the diabetic patients all gave informed consent to participate in this investigation.

The clinical data are summarized in table 1. The fasting blood glucose levels were below 200 mg/dl in all but six subjects and below 300 mg/dl in all but one, whose fasting glucose was 309 mg/dl. Fourteen of 16 diabetics and 10 of 12 normal controls engaged in no regular physical activity; two members of both groups participated in sports.

Methods

Exercise Protocol

The subjects were investigated in the postabsorptive state. No insulin or oral hypoglycemic agents were administered for at least 12 hours before the study. A standard multistage maximal exercise test was conducted on a motorized treadmill according to the Bruce protocol. Standard 12-lead ECGs were obtained at rest in the supine position, after 30 seconds of hyperventilation, during quiet standing, and at 1-minute intervals during the exercise period. Tracings were also recorded immediately after exercise and for each minute during the recovery period, for a total of 8 minutes, or until the heart rate fell below 100 beats/min (a maximum of 10 minutes). Corresponding systolic blood pressure determinations were made at the same time intervals with an Avionics model 1905 variable sensitivity London Pressurometer. Standard blood pressures also were recorded with a Tycos sphygmomanometer during rest and in the postexercise period. The latter could not be obtained with accuracy during peak exercise because of arm motion and excessive noise of the treadmill. Pressure measurements by the two methods did not differ by more than 5 mm Hg. The maximum systolic blood pressure that could be recorded with the pressurometer was 265 mm Hg. Diastolic pressure recordings were also obtained but were subject to greater error during peak exercise with the pressurometer. Exercise was terminated in all subjects because of leg fatigue. There were no episodes of significant arrhythmias, angina, or hypotension.

The exercise ECG was considered abnormal if a horizontal or downsloping ST-segment depression of 1 mm or more occurred 0.08 second after the J point of the QRS complex in any lead during or after exercise.

The following measurements and calculations were made:

1. Predicted maximal oxygen consumption (VO2 max): active males: 69.7–0.612 (age in years); sedentary males: 57.8–0.445 (age in years).

2. Estimated VO2 max (ml/kg/min) (males) = 3.88 + 0.56 (duration in seconds).

3. Functional aerobic impairment:

\[
\text{Predicted } \text{VO2 max} - \text{estimated } \text{VO2 max} \times 100
\]

4. Myocardial oxygen uptake is determined principally by the pressure-rate product. This is determined from the product of the maximal heart rate and the maximal systolic blood pressure (PRP max). Predicted PRP max was derived from the formula: 364 - 0.58 (age in years).

Echocardiography

Technically satisfactory ultrasound studies were obtained in 10 normal control subjects and 14 diabetic patients. The ultrasonic unit consisted of an Irex transducer (2.25 MHz, 1.25 cm in diameter with a 13-cm focal length), an Irex 150-120-01 or Ekoline 20A ultrasonoscope, and a Honeywell 1856 strip-chart recorder. Echocardiograms were performed with the subjects supine or in a partial left lateral decubitus position using a standard intercostal space technique.
to obtain reproducible echocardiograms. The end-diastolic dimension of the left ventricle (LVDD) was measured from the endocardium of the posterior left ventricular wall to the endocardium of the left ventricular septum on the R wave of the ECG. The end-systolic dimension (LVSD) was the minimal distance between the endocardium of the interventricular septum and that of the posterior free wall. All measurements of ventricular dimensions were obtained in the region of or just below the tips of the mitral valve leaflets (fig. 1). Right ventricular dimensions were measured from the right ventricular endocardium to the right side of the septum at end diastole.

The following indexes of myocardial function were derived:

Percent fractional shortening:

$$\frac{LVDD - LVSD}{LVDD} \times 100$$

where LVDD = left ventricular dimension at end-diastole and LVSD = left ventricular dimension at end-systole.

End-diastolic and end-systolic volume from the Teichholz formula:

$$V = \frac{7 \times D^2}{2.4 + D}$$

where $V =$ volume and $D =$ left ventricular dimension.

Ejection fraction = \frac{\text{stroke volume}}{\text{end-diastolic volume}} \times 100

**Radionuclide Scintigraphy**

Thirty seconds before termination of exercise a bolus of 1.25 mCi of thallium-201 was injected through an indwelling venous catheter. This was followed by a flush of 10 ml of normal saline. At the conclusion of exercise, ECGs were taken with the patient lying supine on a stretcher. Immediately after the 8–10 minute postexercise ECG, the patient was transported by wheelchair to the nuclear scanning room and the first scan was begun. This was usually 15 minutes after completion of exercise. Three views were recorded with the subject lying supine in the following sequence: 45° left anterior oblique with a 15° cephalad tilt of the camera, left lateral and anterior. The scintillation camera was a Searle PHO Gamma IV with a parallel-hole, high-resolution collimator. One hundred fifty thousand counts were collected at an energy peak of 70 keV with a 25% window. In addition to making Polaroid films of the osilloscopic image of the scan, scanning information was acquired by a Medical Data Systems Modulated computer system.

When the three views were completed, the Polaroid films were reviewed by one or more of the investigators. If a filling defect was observed, an additional 0.25 mCi of thallium-201 was injected after a rest period of at least 1 hour and the scans in the three views were repeated to determine whether the perfusion defects were reversible. The final interpretation of the scans was made from the Polaroid films aided, in equivocal situations, by a small amount of background subtraction (up to 15%) by the computer.

Blood glucose was obtained in all but one subject.
Statistical evaluation was accomplished by the unpaired \( t \) test.

\textbf{Results}

\textbf{Heart Rate}

The resting supine heart rates were similar in normal and diabetic subjects (67.3 ± 10.2 beats/min and 65.3 ± 11.7 beats/min, respectively). With assumption of the erect position, the heart rate accelerated equally in both groups (to 76.7 ± 16.3 beats/min in the normal subjects and 80.7 ± 17.5 beats/min in the diabetic males). The heart rate at maximal stress was significantly lower in diabetics than in controls (163.1 ± 9.9 beats/min vs 174.5 ± 17.4 beats/min, respectively \( p < 0.05 \)) (table 2, fig. 2). The change in heart rate for diabetic subjects was also less (82.4 ± 20.3 beats/min vs 97.8 ± 14.0 beats/min) in control subjects. \( p < 0.05 \) (table 2). Eleven diabetic subjects and all but one control subject (case 21) achieved 85% of predicted heart rate. Five diabetics had maximal heart rates between 80–95% of the predicted heart rate.

\textbf{Systolic Blood Pressure}

The resting systolic blood pressure in the supine and erect positions in diabetics (118.3 ± 18.5 mm Hg and 125.5 ± 16.9 mm Hg, respectively) was statistically the same as in controls (119.2 ± 11.0 mm Hg and 121.3 ± 14.9 mm Hg). Systolic blood pressures during peak exercise were also the same for both groups (215.9 ± 32.5 mm Hg for the diabetic group and 209.6 ± 21.6 mm Hg for the control group) (table 2). The diabetic males had a slightly higher exercise systolic pressure than their normal counterparts, but this difference did not reach statistical significance. However, blood pressure elevation above 210 mm Hg occurred in only three of 12 normal subjects (25%) but was observed in nine of 16 diabetics (56.2%), including the three with transient pressure elevations before testing.

\textbf{Pressure-Rate Product}

At maximal stress, the pressure-rate product was slightly lower in the diabetic group (348.9 ± 50.6) than in the control subjects (363.7 ± 68.3) (table 2), but the difference was not statistically significant. (This resulted from the lower maximal heart rate despite a higher systolic blood pressure.)

\textbf{Duration of Exercise}

A comparison of the duration of exercise attained by the controls compared with the diabetic males revealed that the latter had a poorer performance on the treadmill (519.0 ± 127.2 seconds) than the former group (663.0 ± 92.1 seconds) \( p < 0.005 \) (table 2, fig. 2).

\textbf{Estimated Maximal Oxygen Consumption}

The maximal oxygen consumption derived from the duration of exertion was also markedly decreased in diabetics (32.9 ± 7.1 ml/kg/min) vs normal subjects (40.6 ± 5.5 ml/kg/min) \( p < 0.005 \) (table 2, fig. 2). Although this parameter was not assessed by direct measurement, we and others have demonstrated that there is close correlation between the direct and estimated oxygen consumption.\(^{16}\)

\textbf{Functional Aerobic Impairment}

The functional aerobic impairment was higher in the diabetics than in normal controls, reflecting their impaired exercise performance \( p < 0.005 \) (table 2, fig. 3).

\textbf{Electrocardiography}

Two diabetic subjects (13.5%) (cases 4 and 13), had significant ST-segment changes. The ST-segment

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Physiologic response to exercise in normal and diabetic subjects. Max HR = maximum heart rate; \( \Delta HR \) = the increase in HR from the basal state to peak exercise; estimated \( VO_{2MAX} \) = maximal oxygen consumption derived from duration of exercise; FAI = functional aerobic impairment. The max HR and \( \Delta HR \) were significantly greater in normal subjects than in diabetics \( p < 0.05 \). There was also a significant difference between normal subjects and diabetics in duration of exercise estimated \( VO_{2MAX} \) and FAI \( p < 0.005 \).}
\end{figure}
Table 2. **Exercise Performance and Myocardial Scintigraphy**

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*p < 0.05, †p < 0.005.

Abbreviations: Max HR = maximal heart rate; ΔHR = change in heart rate; Max SBP = maximal systolic blood pressure; ΔSBP = change in systolic blood pressure; PRP = pressure-rate product; Obs = observed; Pred = predicted; Est VO₂ Max = estimated maximal O₂ consumption; FAI = functional aerobic impairment; ND = not done; INF = inferior; SEP = septum; POST LAT = posterolateral; R = rest; S = stress.

Depressions in case 4 were observed in V₅ at 9 minutes of exercise and did not persist into the postexercise period (fig. 3). Case 14 developed significant ST-segment depressions in leads II, III, and V₆ at 7 minutes of exercise that persisted for 3 minutes into the postexercise period (fig. 4). Only one control subject (8%) (case 21, the oldest member of the group) developed ST-segment depression in leads II, III, aVF,
V5 and V6 at 5 minutes of exercise. These changes persisted in leads V5 and V6 until 7 minutes postexercise.

**Myocardial Scintigraphy**

Thallium-201 scintigraphy in one of the 12 normal subjects was technically unsatisfactory and was excluded. There were perfusion defects on exercise in five of the 12 diabetic males (41.7%) tested with scintigraphy and in one control (case 21). This subject (case 21) also developed positive ST changes (table 2). Three had decreased perfusion of the inferior wall at rest and exercise (cases 2, 9 and 10) (fig. 5), one of the inferior wall and septum at rest and on exercise (case 16), and one of the inferior wall on stress only (case 15) (fig. 6). The control subject (case 21) had a posterior and lateral defect on both stress and exercise. The five subjects with decreased thallium-201 uptake had no electrocardiographic abnormalities on exercise. One of these subjects with a positive scan and negative electrocardiography failed to achieve 85% of the predicted maximal heart rate. Therefore, of 12 diabetic males subjected to maximal exercise testing with thallium-201, seven had either abnormal perfusion with the isotope or significant ST abnormalities. Only one of 12 normal volunteers had either an abnormality of the ECG or a perfusion defect.

**Arrhythmias**

Premature atrial extrasystoles occurred throughout the exercise recovery period in one diabetic subject and frequent ventricular premature systoles occurred throughout the exercise recovery period in another. Frequent ventricular premature systoles were observed at 2 minutes and throughout the exercise period in the control subject with a positive exercise test and abnormal myocardial scintigraphy. No other arrhythmias were observed.

**Echocardiographic Data**

The left ventricular end-diastolic dimensions were similar in both groups (50.5 ± 3.0 mm in normal controls and 49.1 ± 4.1 mm in diabetics) (table 3). End-systolic dimensions were also statistically the same (table 3). The posterior wall thickness was 9.3 ± 1.2 mm for control subjects and 9.0 ± 1.2 mm for diabetics; septal thickness was 8.7 ± 1.3 mm for controls and 9.1 ± 1.4 mm for diabetics (table 3). The right ventricular size was slightly but insignificantly larger in the diabetic males than in the controls (21.5 ± 6.3 mm and 17.9 ± 4.1 mm, respectively). Myocardial function was evaluated by percent fractional shortening, which was slightly less in diabetics (33.9 ± 6.3) than in control subjects (39.0 ± 4.8) (p < 0.05) (table 3, fig. 7). The left ventricular end-diastolic volumes were similar. However, the end-systolic volumes in diabetics were slightly but not significantly greater (42.4 ± 12.9 ml) than in the healthy controls (37.5 ± 9.9 ml) (table 3).

No patient had mitral valve prolapse.
Case 9. Thallium-201 computerized scan. Modified left anterior oblique view demonstrating an area of decreased perfusion of the inferior wall on exercise (A) and rest (B).

Case 15. Thallium-201 computerized scan. Left lateral view demonstrating an area of decreased perfusion of the inferior wall on exercise (A) that is no longer present on rest (B).
TABLE 3. Chamber Dimensions, Wall Thickness and Myocardial Function in Normal and Diabetic Males

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Normal</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>50.5 ± 3.0</td>
<td>49.1 ± 4.1</td>
</tr>
<tr>
<td>LVSD (mm)</td>
<td>30.9 ± 3.4</td>
<td>32.6 ± 4.7</td>
</tr>
<tr>
<td>LVDV (ml)</td>
<td>121.6 ± 15.4</td>
<td>114.1 ± 22.2</td>
</tr>
<tr>
<td>LVSV (ml)</td>
<td>37.5 ± 9.9</td>
<td>42.4 ± 12.9</td>
</tr>
<tr>
<td>RVDD (mm)</td>
<td>17.9 ± 3.9</td>
<td>21.5 ± 6.3</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>9.3 ± 1.2</td>
<td>9.0 ± 1.2</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>8.7 ± 1.3</td>
<td>9.1 ± 1.4</td>
</tr>
<tr>
<td>FS (%)</td>
<td>39.0 ± 4.8</td>
<td>33.9 ± 6.3*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
*p < 0.05.

Abbreviations: LVDD = left ventricular dimension at end-diastole; LVSD = left ventricular dimension at end-systole; LVDV = left ventricular diastolic volume; LVSV = left ventricular systolic volume; RVDD = right ventricular dimension (end-diastole); PWT = posterior wall thickness; IVST = septal thickness; FS = fractional shortening.

Blood Glucose

Blood glucose levels rose significantly in the control subjects (p < 0.02). The glucose was 75.8 ± 9.6 mg/dl in eight control subjects before exercise and rose to 98.5 ± 20.4 mg/dl with exercise (p < 0.05). There was no significant change in blood glucose in the diabetic males (152.3 ± 78.4 mg/dl vs 159.8 ± 86.3 mg/dl).

Discussion

The association between cardiac disease and diabetes has been recognized for many years.1, 2 Previous studies have emphasized the importance of atherosclerosis of the major coronary arteries as a cause of death in the diabetic population. Root et al.26 reported an incidence of coronary artery disease of 38.2% in diabetic males and 32.3% in the females, compared to only 9.9% of 1521 males and 4.9% of 789 females in the same age group. Not only does myocardial infarction occur with greater frequency in those with abnormal carbohydrate metabolism, but the mortality rate after coronary events is higher27 and congestive cardiac failure is more prevalent in these patients.9

Exercise testing with thallium-201 myocardial imaging is a noninvasive method of assessing the high-risk population of middle-aged diabetic males for evidence of latent coronary artery disease. In this study, the exercise performance of these subjects was inferior to that of their nondiabetic peers. The impaired performance could not be attributed to noncardiac causes because none of the subjects had overt myopathy or neurologic disorders. The maximal heart rate and duration of exercise was less in the diabetics than in the control subjects. Their functional aerobic impairment was not as profound as that observed by Bruce27 in a group of older males with ischemic heart disease, but was higher than in the control group. Three of the 16 (18.7%) attained a pressure-rate product below 300 and seven (43.7%) had a functional aerobic impairment of greater than 10% (table 2).

Five of the 12 diabetics with both exercise testing and myocardial scintigraphy had areas of decreased perfusion (four on the exercise and resting scans and one on stress only). The defects on both stress and rest in the four patients were consistent with myocardial scars, probably caused by infarction. In one patient, the defect that appeared only during stress was considered compatible with ischemia. One study (Fisher VJ: unpublished data) evaluated thallium-201 injections in dogs subjected to left anterior descending artery ligation. One group of 10 dogs underwent ligation for 25–28 minutes. Thallium-201 was injected in these dogs at 5 minutes after the initiation of ischemia and again at 5 minutes after the release of the coronary artery ligature. Another group of six dogs with the same ischemic period received only a single dose of thallium-201 at 5 minutes after initiation of ischemia. A final group of six dogs was subjected to sustained ischemia with thallium-201 injected at 5 and again at 20–25 minutes after initiation of ischemia. All 10 dogs that were reinjected after relief of ischemia were found to have a defect on the first myocardial scan that disappeared after the second. In nine this was complete, and in one, only partial. In contrast, the dogs that remained ischemic demonstrated persistent defects on the second scan. The dogs subjected to serial imaging after only one injection did not demonstrate obliteration of the defect by reperfusion after 25 minutes. Thus, as we concluded in our human subjects, when the reinjection technique is used, a defect on stress only is consistent with ischemia, whereas a persistent defect on rest and stress is consistent with infarction.

Although zones of decreased perfusion are also observed in patients with cardiomyopathy, these defects are usually scattered diffusely throughout the myocardium and are usually not discrete areas of decreased uptake. The echocardiographic data (normal left ventricular dimensions, wall thickness, percent fractional shortening) were not consistent with cardiomyopathy.

None of these four diabetics with rest and exercise

PERCENT FRACTIONAL SHORTENING

FIGURE 7. Determination of myocardial function by echocardiography. The data for control and diabetic subjects were within normal range but the former had significantly better function (p < 0.05). Bars indicate mean and SD.
perfusion defects had abnormal ECGs during exercise, although all attained at least 85% of the maximal predicted heart rate. It is possible that although one area of the heart was infarcted, the remainder of the heart was not ischemic. Another explanation for this observation is the insensitivity of exercise electrocardiography alone compared with exercise with myocardial imaging. The absence of electrocardiographic changes in subjects with positive stress thallium scans has been reported previously. The sensitivity of exercise electrocardiography has varied from 45–80%. When myocardial scintigraphy was used in conjunction with electrocardiography in a large multicenter study, sensitivity increased to 91%. In other investigations the sensitivity with exercise electrocardiography alone was 52% and 64%. This improved to 81% and 85%, respectively, when combined with myocardial imaging. In the presence of one-vessel disease, the yield of true-positive results is especially low with electrocardiography alone. Thallium-201 scintigraphy increases the diagnostic accuracy of the test. In subjects such as these, who were asymptomatic and who performed up to 85% of predicted heart rate, one-vessel disease may have escaped detection by stress electrocardiography alone, but old infarcts and ischemia might be revealed by myocardial scintigraphy. The fact that of the five patients with positive thallium-201 scans, four were abnormal on both rest and exercise studies and only one developed the perfusion defect on exercise alone, is interesting. However, this does not eliminate the possibility that in an expanded investigation with a larger population, some subjects may demonstrate defects only on exercise. We are not prepared to state on the basis of our present findings that rest scans alone might suffice for mass screening, although this may be a practical application of this technique in the future.

One control subject with a positive thallium scan had an abnormal electrocardiographic study and poor exercise performance. He was the oldest subject in the group and probably had occult coronary artery disease. The Seattle Heart Watch Study revealed a 16.8% incidence of positive responses in a supposedly healthy male population.

Two diabetic subjects (cases 4 and 14) had abnormal stress ECGs and negative thallium-201 scans. Both patients developed ST-segment depression in the third stage of exercise. These changes persisted into the postexercise period in one subject (case 14) but ceased immediately on termination of exercise in the other. Neither had any functional aerobic impairment. The total assessment of these physiologic and electrocardiographic findings would be consistent with one-vessel or, at most, two-vessel pathology. Although it is possible that these are false-positive results, small areas of ischemia may escape detection by myocardial imaging because (1) collateral flow may be present; (2) the area of reduced perfusion may be too distant from the camera in right coronary or left circumflex artery disease; or (3) overlying myocardium may be well perfused. Rifkin and Hood have demonstrated by the application of Bayesian analysis that the predictive value of the exercise test varies with the prevalence of the disease in the population being studied. The higher the incidence of coronary artery disease, the greater the predictive value of the test. Stearns et al. conducted an autopsy study of diabetics and concluded that "any diabetic man or woman over the age of 40 can be assumed to have advanced coronary disease even in the absence of symptoms, particularly if hypertension is present and more particularly if the disease is more than 10 years' duration." (In one of the patients the diabetes was known to exist for 13 years.) The ultimate proof rests with coronary arteriography, but this procedure could not be justified in asymptomatic subjects.

The systolic blood pressure at maximal exertion was higher in the diabetic males than in their normal peers, although the difference was not statistically significant. More than half the diabetics had an increase in pressure in excess of 210 mm Hg and only 25% of the control subjects had elevations to this level. These exaggerated pressure responses may indicate decreased compliance of the vascular system in aging diabetics.

The overall decrease in exercise performance in this group of diabetics may suggest not only major coronary artery disease but may result from pathologic changes in the small arterioles or the myocardium itself. An interstitial deposition of glycoprotein-like material that is PAS-positive has been observed surrounding small arteries. Localized fibrosis and dense collagen networks have resulted in the destruction of myofibrils. Biochemical analysis of cardiac muscle has revealed increased triglyceride and cholesterol concentration without changes in phospholipid. In a recent study of 21 juvenile-onset diabetics with severe renal insufficiency and no cardiac symptoms, severe coronary artery disease was found on arteriography in nine patients; two others had diffuse myocardial disease with no coronary artery pathology. The authors concluded that coronary arteriography was essential for the detection of cardiac disease in asymptomatic diabetics undergoing hemodialysis. Although this may be imperative in those with advanced renal pathology, the identification of heart disease in diabetic subjects with few or no complications could be evaluated by using noninvasive screening methods to preclude the risk of such invasive procedures in asymptomatic individuals. During exercise, the appearance of abnormal electrocardiographic changes and/or perfusion defects in conjunction with an impaired exercise performance or an excessive rise in systolic blood pressure may be useful in identifying those who will develop overt cardiac disease in the future. In addition, those individuals who demonstrate defects on both rest and stress thallium-201 studies may have already sustained myocardial infarctions that are frequently silent in diabetics. Long-range studies are required to define the prognostic significance of these abnormalities.
Addendum

Case 7 was restudied after 1 year with stress electrocardiography and myocardial imaging with thallium-201. His resting supine blood pressure was 115/85 mm Hg during his first test, but the maximal systolic pressure rose to 265 mm Hg (no myocardial scintigraphy was performed). During the interval between studies, he developed sustained hypertension and on his second test, his baseline pressures were 200/105 mm Hg in the supine position and 200/110 mm Hg on standing. The resting ECG revealed new Q waves in V6 and V4, not noted on his initial test. His pressure again rose to 265 mm Hg with exercise; the heart rate at maximal exertion was 162 beats/min, compared with 165 beats/min during the first study and his duration of exercise (438 seconds), functional aerobic impairment and estimated maximal oxygen consumption were the same as they were 1 year earlier. A thallium-201 perfusion scan revealed decreased uptake of the inferior wall on exercise, which only partially resolved during rest consistent with ischemia superimposed on an old scar.

References

Relationship Between Clinical Features of Acute Myocardial Infarction and Ventricular Runs 2 Weeks to 1 Year After Infarction

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SUMMARY Ten-hour electrocardiographic (ECG) monitoring was performed on 289 survivors of myocardial infarction (MI) at 2 weeks, at monthly intervals for 6 months and then at 9 and 12 months after MI. Four hundred thirty episodes of ventricular runs were recorded on 88 patients (30%). The clinical features during the acute phase of MI of these 88 patients were evaluated prospectively and compared with those of patients who did not have runs. Both groups were similar with respect to age, sex and preexisting coronary risk factors. However, patients with runs had higher peak serum enzyme levels and a higher prevalence of congestive heart failure, cardiomegaly and left ventricular hypertrophy. They also had more frequent atrial premature complexes, premature ventricular complexes at a rate of 6/min or more, and ventricular conduction defects during the acute infarction. The presence of runs within 3 months after the MI was predictive of the presence of runs during the period 4–12 months after MI. Using a multivariate logistic analysis patients could be divided into quartiles of risk for posthospital runs on the basis of features noted during the acute phase. The prevalence of runs ranged from 4% in the lowest quartile to 49% in the highest one. Although the rate of sudden death was not different in each quartile of risk of having ventricular runs, patients in the highest quartile had a significantly higher mortality rate (16.7%) than those in the lowest one (5.6%). We conclude that severe cardiac disease manifested by poor left ventricular function, high serum enzyme levels, and certain types of cardiac arrhythmias during acute MI are associated with an increased prevalence of ventricular runs during the posthospital phase. Our study suggests that the higher mortality rate in the highest quartile of risk of having ventricular runs is related to severe cardiac disease rather than to the presence of the runs.

Runs of ventricular ectopic activity (VEA) often occur in the course of acute myocardial infarction (MI) and usually call for immediate initiation of antiarrhythmic or other therapy.1 However, some patients continue to have ventricular runs (three or more consecutive beats of VEA) during recovery from their MI.2–4 Several investigators5–7 have reported that the occurrence of these runs is associated with an increased risk of sudden cardiac death. However, little is known about how to identify patients who are likely to develop runs. Symptoms reported by patients cannot be used as a guide because runs are, for the most part, asymptomatic.3 Some studies5–7,8 have relied on ECG recordings of brief duration (1–6 hours) to detect the occurrence of VEA. Frequently, only a single ECG recording is obtained just before the time of discharge or in the immediate posthospital period. Patients might be free of VEA on this recording and yet have it a month later. Therapy would be more likely initiated if the physician were aware that these patients are having runs. Thus, more should be known about the prevalence of these runs and the patients who are likely to have them.

Repeat ECG monitoring at monthly intervals can be used as a research endeavor, but is not a practical way of identifying patients who will develop runs. If one could identify the patients prone to having runs during the posthospital phase from information readily attained during their hospital stay, such patients could be further investigated with ECG
Exercise testing with myocardial scintigraphy in asymptomatic diabetic males.
T Abenavoli, S Rubler, V J Fisher, H I Axelrod and K P Zuckerman

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