Decreased Exercise Heart Rate and Blood Pressure Response in Diabetic Subjects With Cardiac Autonomic Neuropathy

JOEL K. KAHN, MD, BENJAMIN ZOLA, MD, JACK E. JUNI, MD, AND AARON I. VINIK, MD

Abnormal hemodynamic responses to exercise have been observed in diabetic subjects, but the pathogenesis and significance remain uncertain. We used maximal treadmill exercise to study 32 subjects with long-term insulin-dependent diabetes without clinical evidence of cardiac disease. Two of the 32 had occult ischemic heart disease revealed by stress electrocardiography and myocardial-perfusion scintigraphy and were excluded from subsequent analysis. In the remaining 30 subjects, we compared the responses to exercise of the 17 subjects with cardiac autonomic neuropathy diagnosed by noninvasive maneuvers (group 1) with the 13 without (group 2). At rest, the pressure-rate product (PRP) was higher in group 1 (114.0 ± 5.7 vs. 95.9 ± 5.3, $P < .05$). With maximal exercise the increase in heart rate (44.6 ± 4.8 vs. 79.0 ± 5.4 beats/min, $P < .001$), systolic blood pressure (36.8 ± 5.9 vs. 55.0 ± 5.8 mmHg, $P = .02$), and the PRP (102.0 ± 7.3 vs. 182.0 ± 8.2, $P < .001$) were all lower in group 1 than in group 2, despite similar total treadmill times (631 ± 47 vs. 587 ± 40 s, $P > .1$). At each stage of exercise, the increase in heart rate and systolic blood pressure was lower in group 1 patients. The severity of cardiac autonomic neuropathy correlated inversely with the maximal increase in heart rate ($r = -.68$, $P < .001$) and the PRP ($r = -.58$, $P < .005$). Age, duration of diabetes, and the presence and severity of microvascular disease did not correlate with any of the hemodynamic parameters. Thus, cardiac autonomic neuropathy is associated with an impairment of the hemodynamic responses to exercise in diabetic subjects without ischemic heart disease. DIABETES CARE 1986; 9:389–94.

Autonomic nervous system reflexes are important in the cardiovascular responses to exercise,[1,2] and abnormalities in the function of the autonomic nervous system would be expected to result in deranged regulation of the response to exercise. Impairment of autonomic nervous system activity in patients with long-term diabetes mellitus has been recognized for over 40 yr,[3] and although the exercise response in subjects with diabetes mellitus has been characterized,[4–8] few studies have examined the impact of the autonomic neuropathy of diabetes on the exercise response.[9,10] Because of rising interest and enthusiasm for exercise training as a modality in the multidisciplinary approach to the therapy of diabetes mellitus,[11] we felt that further investigation in this area was warranted. We have prospectively studied the cardiovascular response to graded treadmill exercise in a group of insulin-dependent diabetic subjects with carefully characterized autonomic nervous system function. We excluded ischemic heart disease insofar as possible so as not to confound interpretation of the data. Our results indicate that cardiac autonomic neuropathy is associated with significant alterations in the cardiovascular response to exercise and must be considered in planning this form of therapy.

PATIENTS AND METHODS

Patient population. Thirty-two subjects ranging in age from 19 to 45 yr were prospectively entered into the study. Twenty-two of the subjects were women, and 10 were men. The duration of diabetes mellitus ranged from 10 to 28 yr. All subjects signed an informed consent approved by the Human Use Committee of the University of Michigan Medical Center.

Subjects were selected by the following criteria: *1*) insulin-dependent diabetes mellitus for ≥10 yr; 2) no clinical evidence of coronary artery disease, prior myocardial infarction, congestive heart failure, or hypertension; 3) creatinine clearance ≥75 cm^3/min; and 4) absence of intercurrent illness

TABLE 1
Diabetic complication score scale

Retinopathy
- 0 = Absent
- 1 = Mild background changes
- 2 = Severe background changes and intraretinal microvascular abnormalities
- 3 = Proliferative changes

Nephropathy
- 0 = <150 mg urinary protein/24 h
- 1 = 150–500 mg urinary protein/24 h
- 2 = >500 mg urinary protein/24 h

Neuropathy
- 0 = Absent
- 1 = Absent ankle jerks; stocking-glove hypoalgesia or hypoanesthesia
- 2 = More severe involvement: weakness, paralysis, or analgesia or anesthesia

such as ketosis, acidosis, infection, or a recent hypoglycemic episode. All medicines other than insulin were discontinued 48 h before testing. None of the subjects were well-trained athletes.

The presence and severity of diabetic complications were identified and graded for each subject by a diabetic complication score modified from that of Shapiro,[12] ranging from 0 to a maximum score of 7 (Table 1). Patients were screened for cardiovascular autonomic neuropathy by use of five noninvasive maneuvers established as reproducible indices of autonomic nervous system activity.[13,14] Patients were scored from 0 to 5 based on the number of abnormal tests and were classified as having definite cardiovascular autonomic neuropathy if two or more tests were abnormal, in agreement with the criteria of Ewing et al.[14] The tests included the following: *1*) Resting heart rate: the heart rate was determined after each subject had been supine for 15 min; abnormal was defined as ≥100 beats/min. *2*) Beat-to-beat variability: the difference between the minimum and the maximum heart rate was determined from electrocardiographic tracings during periods of inspiration and expiration with subjects breathing 6 times/min; abnormal was defined as a difference of ≤10 beat/min. *3*) Valsalva maneuver: the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver was determined from electrocardiographic tracings, with subjects blowing into a manometer maintaining 40 mmHg for 15 s; abnormal was defined as a ratio ≤1.10. *4*) Heart rate response to standing: during electrocardiographic monitoring, the ratio of the R-R interval at the 30th beat after standing to the R-R interval at the 15th beat (30:15) was determined; abnormal was defined as a ratio ≤1.00. *5*) Blood pressure response to standing: the fall in systolic blood pressure after 1 min of standing was determined by cuff sphygmomanometry; abnormal was defined as a fall ≥30 mmHg.

TABLE 2
Exercise protocol

Time (min)	Stage	Speed (mph)	Grade (%)
1–3	1	1.7	10
3–6	2	2.5	12
6–9	3	3.4	14
9–12	4	4.2	16
12–15	5	5.0	18

Catecholamine determination. A polyethylene cannula was placed in an antecubital vein with a heparin lock. Blood samples were collected after 30 min with the subject in the supine position and again 15 min after standing. Plasma norepinephrine concentration was measured by the method of Peuler and Johnson.[15]

Exercise protocol. Subjects were studied in the postabsorptive state. A standard maximal staged exercise test was conducted on a motorized treadmill according to the protocol of Bruce (Table 2).[16] Standard 12-lead ECGs were obtained at rest in the supine position, during quiet standing, after 30 s of hyperventilation, and 2 min into each exercise stage. Tracings were also recorded every 2 min in the recovery period until the heart rate returned to baseline. Corresponding systolic blood pressures were recorded with a cuff sphygmomanometer at rest, 2 min into each exercise stage, and during the recovery stage. The amplitude of the R wave in lead V_5 was measured with calipers for three consecutive sinus beats and averaged both at rest and at peak exercise. The exercise ECG was considered abnormal if a horizontal or downsloping S-T segment depression of 1 mm or more occurred 0.08 ms after the J point of the QRS complex in any lead during or after exercise. The predicted PRP was derived from the formula 364 − 0.58 (age in yr).[17]

Myocardial perfusion scintigraphy. To further exclude abnormalities of coronary perfusion in our subjects, thallium-201 scintigrams were obtained.[18] One minute before the ter-

TABLE 3
Clinical characteristics of subjects divided according to presence or absence of cardiac autonomic neuropathy

	Without (*N* = 15)	With (*N* = 17)
Age (yr)	33.5 ± 2.7	32.8 ± 1.6
Diabetes (yr)	18.1 ± 1.4	16.8 ± 1.3
Height (in)	66.2 ± 1.7	67.0 ± 0.7
Weight (lb)	141.1 ± 6.7	142.2 ± 6.9
Cholesterol (mg/dl)	194.4 ± 13.8	166.4 ± 13.1
Triglyceride (mg/dl)	123.9 ± 9.9	112.0 ± 6.8
Diabetic ketoacidosis (total episodes)	19.1 ± 2.0	16.8 ± 1.3
HbA_1*(g/dl)	9.3 ± 0.7	10.0 ± 0.5
Diabetic complication score†	2.6 ± 0.5	3.3 ± 0.5
Basal norepinephrine (pg/ml)	331.1 ± 84.8	250.0 ± 38.4
Standing norepinephrine (pg/ml)	531.9 ± 47.5	425.4 ± 103.1

*Nondialyzable glycosylated HbA_1.
†See text.

mination of exercise, 3 mCi i.v. of thallium-201 chloride was injected followed by a saline flush. Immediately after the recovery period, tomographic images were obtained with a rotating γ-camera. Images were acquired over a 180° arc and were reconstructed with a convolution-backprojection algorithm to yield transverse, short-axis, and horizontal and vertical long-axis sections. Imaging was repeated 3 h after exercise in a similar manner. Scans were interpreted by two independent nuclear medicine specialists and were considered indicative of ischemic heart disease if there were any fixed or reversible perfusion defects.

Statistical methods. Data were entered into the CLINFO database of the University of Michigan Clinical Research Center, and significance was evaluated with the Wilcoxon rank-sum test. Correlations were tested by analysis of the goodness of fit by the method of least mean squares. A P value of $<.05$ was considered significant; NS indicates nonsignificant. Data are expressed as the mean ± SE.

RESULTS

Autonomic Testing

Seventeen of the 32 diabetics were classified as having cardiac autonomic neuropathy by the indices of autonomic function described above. The diabetics with cardiac autonomic neuropathy were similar to those without neuropathy in all parameters measured (Table 3). Supine and upright catecholamine measurements were not significantly different between the two groups (Table 3).

Exercise Electrocardiography and Perfusion Scintigraphy

Five subjects had exercise terminated due to the attainment of the target heart rate for age, 25 elected to terminate exercise due to leg fatigue, and 1 due to shortness of breath. One subject developed chest pain and 2 mm downsloping S-T depression in leads V_5 and V_6. Due to the likelihood of ischemic heart disease in this patient, she was excluded from subsequent analysis of hemodynamic data.

Myocardial perfusion scintigraphy was completely normal in 30 of the remaining 31 subjects. One subject free of microvascular complications or cardiac autonomic neuropathy developed decreased tracer uptake with partial redistribution on delayed images. This patient was also excluded from subsequent analysis.

In the 30 remaining subjects without evidence of ischemic heart disease, the change in amplitude of the R wave in lead V_5 from rest to peak exercise ranged from a 5-mV increase to a 9-mV decrease. Twenty-nine of the 30 subjects exhibited a decrease in the amplitude of the R wave with exercise. The R-wave amplitude increased in both diabetics with evidence of ischemic heart disease.

Hemodynamic Response to Exercise

Resting hemodynamics. Of the 30 remaining diabetics without evidence of ischemic heart disease, 17 had evidence of cardiac autonomic neuropathy, and 13 were free of such abnormalities. At rest, the heart rate and PRP were higher among the diabetics with cardiac autonomic neuropathy, but the systolic blood pressure was comparable (Table 4).

TABLE 4
Hemodynamic response to exercise in diabetic subjects with and without cardiac autonomic neuropathy

	Without (N = 13)	With (N = 17)
Heart rate (beats/min)		
At rest	79 ± 4	90 ± 2*
Maximal	158 ± 5	136 ± 6†
Increment	79 ± 5	45 ± 5†
Systolic pressure		
At rest	121 ± 4	123 ± 6
Maximal	176 ± 8	158 ± 7†
Increment	55 ± 6	37 ± 6*
Pressure-rate product		
At rest	96 ± 5	114 ± 6*
Maximal	278 ± 13	216 ± 14†
Incremental	172 ± 8	102 ± 5†

*$P < .05$; †$P < .01$

Duration of exercise. Both the stage of the Bruce protocol completed (3.4 ± 0.7 vs. 3.5 ± 0.3, P = NS) and the total exercise time (631 ± 47 vs. 587 ± 40 s, P = NS) were comparable between the diabetics with and without cardiac autonomic neuropathy, respectively. Of the 13 diabetics without autonomic neuropathy, 1 completed stage 2 of the Bruce protocol, 6 completed stage 3, 5 completed stage 4, and 1 completed stage 5. Of the 17 diabetics with autonomic neuropathy, 3 completed stage 2 of the protocol, 5 completed stage 3, 8 completed stage 4, and 1 completed stage 5.

Heart rate response. The maximal heart rate obtained at peak exercise by the diabetics with cardiac autonomic neuropathy was lower than that achieved by those free of autonomic neuropathy (Table 4). Because of their higher resting heart rate, the change in heart rate from rest to peak exercise was also lower among the diabetics with autonomic neuropathy. At each stage of exercise, the heart rate was lower in the diabetics with cardiac autonomic neuropathy (Figure 1). The autonomic function score correlated with the peak heart rate ($r = -.51$, $P < .005$) and the change in heart rate ($r = -.68$, $P < .001$; Figure 2). The correlation of the cumulative autonomic function score with the measurements of heart rate was stronger than with any of the individual indices of autonomic function (data not shown). Patient age, duration of diabetes, and the diabetic complication score did not correlate with the peak heart rate or the change in heart rate.

Systolic blood pressure response. The maximal systolic blood pressure at peak exercise was lower in the diabetics with cardiac autonomic neuropathy (Table 4). The change in systolic blood pressure was also lower in this group. At each individual stage of exercise other than stage 1, the systolic blood pressure was lower in the diabetics with cardiac autonomic neuropathy (Figure 1). The autonomic function score did not correlate with the maximal systolic blood pressure ($r = -.253$, P = NS) but approached significance in re-

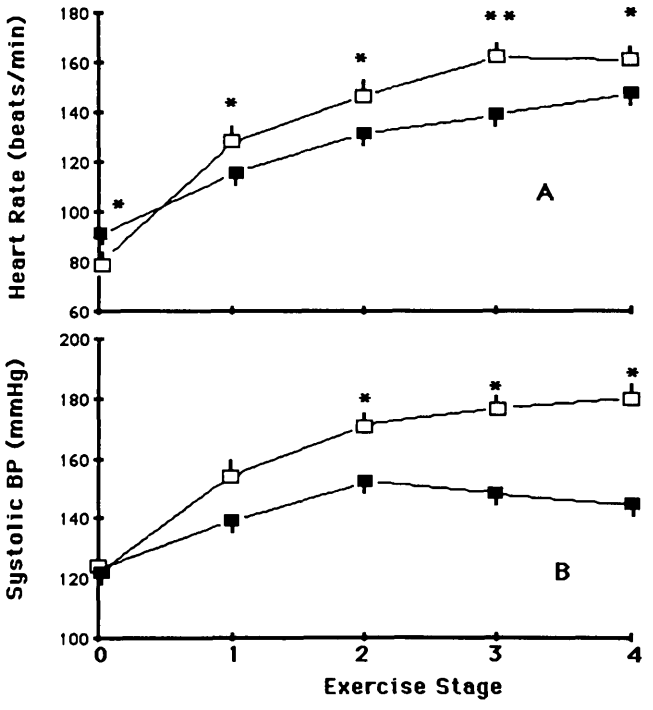

*FIG. 1. A: heart rate at rest and at each stage of Bruce protocol treadmill test in 30 subjects with insulin-dependent diabetes mellitus with (■) and without (□) cardiac autonomic neuropathy. Data expressed as mean ± SE. B: systolic blood pressure at rest and at each stage of Bruce protocol treadmill test in 30 subjects with insulin-dependent diabetes mellitus. Symbols are same as in A. *P < .05; **P < .01.*

lation to the change in systolic blood pressure ($r = -.322$, $P = .08$). Patient age, duration of diabetes, and the diabetic complication score did not correlate with measurements of blood pressure.

PRP Response. The predicted maximum PRP for the two groups was similar (344.5 ± 1.5 vs. 344.0 ± 0.9, P = NS). The maximal PRP achieved by the diabetics with cardiac autonomic neuropathy was lower (Table 4), and the percent of predicted PRP achieved was correspondingly lower in this group (62.0 ± 4.1 vs. 81.0 ± 3.9%, $P < .005$). The change in PRP from rest to exercise was also lower in the diabetics with cardiac autonomic neuropathy (Table 4).

DISCUSSION

We have analyzed two groups of diabetic subjects similar in all parameters measured except for the presence of cardiac autonomic neuropathy in one of the groups as determined by a battery of noninvasive indices of autonomic activity. Both groups were without symptomatic, electrocardiographic, or scintigraphic evidence of ischemic heart disease. The main finding was that in diabetic subjects wtih cardiac autonomic neuropathy, the response to dynamic exercise was impaired compared with diabetic subjects free of such autonomic neuropathy. Despite similar exercise duration, significantly smaller increases in heart rate and arterial pressure at each level of graded exercise were observed in the diabetic subjects with cardiac autonomic neuropathy. Furthermore, significant correlations were found between the entire range of the autonomic function score utilized and the cardiovascular responses measured. No similar correlations were found between exercise responses and patient age, duration of diabetes mellitus, or the severity of diabetic microvascular complications.

By performing exercise electrocardiography and myocardial perfusion scintigraphy, abnormalities consistent with ischemic heart disease have been demonstrated in 16–58% of diabetic subjects without clinical evidence of ischemic heart disease.[19,20] Chin and co-workers[21] have described chronotropic incompetence among patients with coronary artery disease, and Eckberg and colleages[22] have characterized a defect in parasympathetic function in patients with coronary artery disease.

We therefore performed stress electrocardiography and perfusion scintigraphy in all of our subjects and omitted the two (6%) with abnormal findings to virtually exclude any influence of concommitant coronary artery disease on the interpretation of the hemodynamic data. Further evidence against coronary artery disease in our patients was the response of the amplitude of the R wave during exercise. Although not universally accepted, it has been shown that in normal subjects, the R-wave amplitude decreases during exercise,[23] perhaps due to diminished ventricular volume,[24] whereas in patients with coronary artery disease, there is no change or increase in the amplitude of the R wave.[25] In our diabetic subjects, 29 of the 30 subjects without evidence of ischemic heart disease had a normal decrease in the amplitude of the R wave with exercise, whereas both subjects with evidence

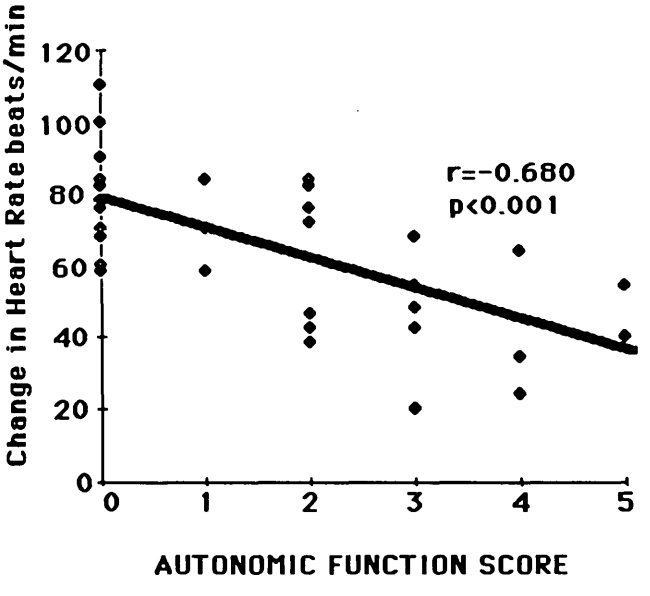

FIG. 2. Regression analysis of maximal exercise-induced change in heart rate on autonomic function score in 30 subjects with insulin-dependent diabetes mellitus (see text).

of ischemic heart disease had an increase in the R wave with exercise.

Our findings are in agreement with the currently understood role of the autonomic nervous system in controlling the cardiovascular response to exercise. The increase in heart rate that occurs during exercise results from an interaction of the parasympathetic and sympathetic limbs of the autonomic nervous system. At low work loads, the increase in heart rate appears to be due to the withdrawal of vagal efferent tone,[26] whereas at higher work loads, the maximal heart rate appears to be due to sympathetic system activation of the sinoatrial node.[27] The significant correlation of the cumulative autonomic function score with the exercise-induced increase in heart rate lends further support to the concept of defective autonomic innervation of the heart in subjects with abnormal noninvasive autonomic function tests.

In normal subjects, arterial pressure increases during submaximal and maximal exercise, despite decreases in total peripheral resistance. The increase in arterial pressure despite vasodilation in exercising muscle groups reflects regional increases in vascular resistance, predominantly in the splanchnic and renal beds.[1] The decreased flow to these areas is mediated by the sympathetic nervous system and can be inhibited by α-adrenergic blockade.[1] As degeneration of sympathetic fibers has been demonstrated in the splanchnic bed of diabetics,[28] it would be anticipated that impairment of sympathetically mediated splanchnic vasoconstriction in diabetics would result in a blunted rise in blood pressure during exercise. We observed such a phenomenon in our subjects with autonomic neuropathy but not in those with intact autonomic nervous system activity. Because only one of the indices of autonomic function in our battery (orthostatic blood pressure) involves a reflex arc involving predominantly sympathetic pathways,[14] it is not surprising that the correlation of the cumulative autonomic function score with the blood pressure response to exercise was weaker than that for the heart rate response.

An additional explanation for the blunted blood pressure response to maximal exertion in the subjects with cardiac autonomic neuropathy is the possibility of underlying myocardial dysfunction in this group. Diminished stroke volume at rest and with exercise has been observed in diabetic patients with extensive autonomic neuropathy,[10] and we have demonstrated that diabetic subjects with cardiac autonomic neuropathy have depressed left ventricular ejection fractions at rest and with exercise compared with those free of autonomic neuropathy.[29] Diminished stroke volume and impaired cardiac acceleration would be expected to result in a decrease in cardiac output, a primary determinant of arterial pressure.

Hilsted and co-workers[9] found similar responses in 13 diabetic patients, 7 of whom had abnormal autonomic function testing. They observed that the increase in heart rate with exercise was lower among those with autonomic neuropathy, and a strong correlation of impaired beat-to-beat variability to the change in heart rate with exercise was described. They did not find an impairment in the blood pressure response to exercise in their subjects, but in a later study, involving 7 subjects with more extensive autonomic neuropathy, a reduction in the systolic blood pressure response to exercise was seen.[10]

Interestingly, exercise duration in the group with cardiac autonomic neuropathy was similar to subjects without definite cardiac neuropathy. This observation is tempered by the fact that maximal oxygen uptake was not measured and may not have been comparable between the two groups, although nomograms would predict similar values.[30] On the basis of impaired cardiac acceleration in patients with cardiac autonomic neuropathy, in addition to the possibility that the increase in stroke volume with exercise may have been abnormal in our patients similar to the subjects studied by Hilsted et al.,[10] a diminished cardiac output in response to exercise would have been predicted with the earlier onset of fatigue. It is possible that stroke volume in response to exercise was perserved in our patients in contrast to those studied by Hilsted et al.[10] because of differences in patient selection. Alternatively, differences in efficiency of oxygen extraction or oxygen utilization by exercising muscles may exist between diabetics with and without cardiac autonomic neuropathy. More likely, however, this observation reflects the fact that exercise tolerance represents the complex interplay of many factors, including chronotropic competency, tolerance of elevated cardiac filling pressures, ventricular dilation, augmented stroke volume, and elevated circulating catecholamines.[31] Further studies assessing all of these parameters will be required to further explore this interesting observation.

In conclusion, the presence of cardiac autonomic neuropathy as determined by a battery of simple noninvasive maneuvers identifies a group of diabetic patients with a significant impairment of the normal heart rate and blood pressure response to exercise. These alterations are not associated with ischemic heart disease and may reflect diminished parasympathetic and sympathetic control of the sinoatrial node and vascular resistance beds, as well as a possible underlying diabetic cardiomyopathy. These findings not only enhance our appreciation of the natural history and pathophysiology of diabetic autonomic neuropathy but may also have a role in the planning of prudent exercise programs for subjects with diabetes mellitus interested in physical training. Specifically, the use of age-predicted maximal heart rates as a goal in exercise training programs in these patients would probably be inappropriate.

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From the Department of Internal Medicine, the Division of Endocrinology and Metabolism, the Division of Nuclear Medicine, and the Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan.

Address reprint requests to Aaron I. Vinik, MD, University of

Michigan Medical Center, 2922B Taubman Health Care Center, Ann Arbor, MI 48109.

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