Subclinical Left Ventricular Abnormalities in Young Diabetics*

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Twenty young asymptomatic diabetic patients were evaluated for left ventricular dysfunction by determining the radionuclide ejection fraction response to supine bicycle ergometry. The double product at peak exercise (28,743 ± 3,314 vs 29,007 ± 3,625, p > .05) was not significantly different between the two groups. Seven of 20 diabetics had either no change or a drop in their ejection fraction during exercise while 1 of 20 control subjects had no change in ejection fraction. There was no correlation between the FBS (r = .26) and HbA1c (r = .32) and ejection fraction change during exercise, although those diabetics with LV dysfunction tended to have a higher HbA1c level as compared to diabetics with a normal response (16.8 ± 3.1 percent vs 12.5 ± 3.8 percent respectively, p > .05). The LV systolic dysfunction in young asymptomatic diabetic subjects does not appear to correlate with the degree of acute or chronic hyperglycemia, and therefore, is not a direct function of the dynamic metabolic state of diabetes.

Subclinical left ventricular (LV) dysfunction may be seen in normotensive, asymptomatic diabetic patients who have no objective evidence of coronary artery disease.1-6 These changes, over time, may be responsible for the higher than expected incidence of congestive heart failure.7-8 The pathogenesis of these changes that occur in some but not all diabetics is unclear. Necropsy and animal studies indicate that diffuse myocardial ischemia and scarring may occur as a result of microvascular coronary artery involvement,9-11 while others suggest that compliance and contractility of the left ventricle may be mediated by myocardial glycoprotein deposition12,13 or from the metabolic functional abnormalities secondary to hyperglycemia itself.14-16 Experimental data show that these morphologic or functional changes may be related to the degree of diabetic control,15-17 and that therapeutic intervention may prevent or reverse these abnormalities.16,17 A similar association has only been alluded to in humans.18,19 The purpose of this study is to evaluate LV function in young asymptomatic diabetic patients and to determine if changes in LV performance could be related to the level of diabetic regulation.

METHODS

Twenty diabetic subjects, ten men and ten women, whose mean age was 32 ± 7 years (range 19 to 44 years) were selected from both an inpatient and outpatient population for an exercise stress MUGA study. Twenty normal volunteers, ten men and ten women, with a mean age of 32 ± 6 years (range 22 to 42 years) served as control subjects. None of the diabetic or control subjects had a past or present history of cardiac disease or symptoms, and results of current physical examinations and electrocardiograms (ECG) were normal. Risk factors for coronary artery disease, such as hypertension, cigarette smoking, and a past family history of coronary artery disease were absent in both the study and control subjects. With the exception of two diabetic subjects, all individuals had total serum cholesterol levels below 250 mg/dl.

We considered diabetic subjects to have microangiopathy if either retinopathy or nephropathy was present. Patients underwent direct ophthalmoscopic examination after dilatation of the pupils. Diabetic retinopathy was diagnosed on the basis of dot and blot hemorrhages, multiple hard exudates, neovascularization or fibrotic changes alone or in any combination.20 Proteinuria greater than 500 mg/24 hours was considered an indication of diabetic renal involvement in the absence of infection, congestive heart failure, or known prior renal disease.

A resting and exercise radionuclide ventriculogram was acquired during a supine symptom-limited bicycle ergometer stress test at a graded workload calibrated in kilopounds (kpm) following i.v. labeling of red cells with 99mTc. Four millicuries of stannous pyrophosphate was injected 20 minutes prior to an injection of 25 mCi of 99mTc through an antecubital vein. Workload was initially started at 400 kpm/minute for men and 200 kpm/minute for women. The workload was increased by 200 kpm every four minutes while the pedal speed was maintained at 50 revolutions per minute. Exercise was considered adequate if the heart rate exceeded 80 percent of the predicted normal for age21 or the rate-pressure product was greater than 55 percent and an increase of at least 3 percent during peak exercise has been established as normal values in our laboratory. Prior to exercise, an FBS and HbA1c level were drawn.

Blood pool imaging was performed with an imaging gamma camera fitted with a multipurpose collimator and interfaced with a digital computer system. The camera was positioned in the 250 to 450 left anterior oblique position with enough cardiac tilt of the camera to separate the ventricles from the aorta. Count image acquisition was made toward the end of each four-minute exercise stage and between the second and fourth minute in the recovery stage. Data were recorded in a 64 × 64 matrix, and the average cardiac cycle was divided into 16 frames. Radionuclide data analyses were performed using a semiautomatic edge detection program. Radioactive counts were calculated throughout the cardiac cycle while a fixed region of background counts was eliminated to improve the signal-to-noise ratio. The end-systolic and end-diastolic frames were identified from the time activity curve. Separate left ventricular end-systolic, and end-diastolic regions of interest were defined.

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by joy stick manipulation. Segmental wall motion was assessed qualitatively by two independent observers using an endless loop cine format for review. Wall motion was classified as normal, hypokinetic, akinetic, or dyskinetic.

Statistical analysis was performed by the Student's t-test for unpaired data. Values are expressed as the mean standard deviation. A p value of <.05 was considered significant. Correlations between the diabetic state (FBS and HbaA1c levels) and the exercise ejection fraction response were calculated by means of linear regression coefficients.

**RESULTS**

**Clinical Data**

Seventeen of the 20 diabetic subjects were insulin-dependent. Two were receiving oral agents and one was treated by diet alone. Nine subjects had signs of diabetic angiopathy with typical retinopathy and/or proteinuria. The average duration of diabetes was 12 ± 8 years (range 1 to 27 years [Table 1]).

**Exercise Stress Test**

Exercise performance was better in the control group than the diabetic group (Tables 1 through 3). The peak heart rate response (83 ± 8 percent of predicted normal for diabetic vs 91 ± 4 percent for control subjects, p<.0001), and the time of exercise (12 ± 4 minutes for diabetics vs 17 ± 5 minutes for control subjects; p<.01) was significantly higher in the control group. However, the double product at peak exercise was not significantly different between the two groups (28,743 ± 3,314 vs 29,007 ± 3,625, p>0.05 for diabetic and control subjects, respectively). Two of the diabetic and three of the control subjects failed to reach a double product of at least 25,000. Systolic blood pressure at peak exercise was significantly higher in diabetics (187 ± 20 mm Hg vs 167 ± 20 mm Hg for diabetics vs control subjects, respectively, p<.001).

Seven patients in the diabetic group had either no change (one) or a decrease in the ejection fraction (six) at peak exercise, as compared to their resting ejection fraction value (Fig 1). There were no ST segment changes on the resting ECG which suggested ischemia. The remaining 13 patients had at least a 3 percent increase in their ejection fraction at peak exercise.

**Table 2—Normal Control Subjects***

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>PPCHR (%)</th>
<th>Peak BP (mm Hg)</th>
<th>Rest EF (%)</th>
<th>Peak EF (%)</th>
<th>Change in EF (%)</th>
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<td>82</td>
<td>160/80</td>
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<td>74</td>
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<td>2, F</td>
<td>58</td>
<td>88</td>
<td>170/92</td>
<td>25,500</td>
<td>58</td>
<td>65</td>
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<tr>
<td>3</td>
<td>3, F</td>
<td>74</td>
<td>92</td>
<td>150/70</td>
<td>25,800</td>
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<td>4, F</td>
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<td>88</td>
<td>160/70</td>
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<td>57</td>
<td>11</td>
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<td>2, M</td>
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<td>62</td>
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*Same abbreviations as for Table 1.
(range 3 to 22 percent). Nineteen of the 20 control subjects showed an increase in the ejection fraction of 3 percent or more (range 3 to 23 percent). A female control subject had no change in ejection fraction at peak exercise. None of the diabetic or control subjects developed regional wall motion abnormalities during exercise.

There was no correlation between the ejection fraction response to exercise and the fasting blood sugar ($r=0.26$) or the HbA1c level ($r=0.32$). There was also no statistical difference in HbA1c levels between diabetics with an abnormal ejection fraction response (17 ± 3 percent) and those with a normal response (13 ± 4 percent).

The incidence of angiopathy was similar in diabetics with or without an abnormal ejection fraction response to exercise (three of seven [43 percent] versus six of 13 [46 percent], respectively). The duration of diabetes mellitus (10 ± 6 years vs 14 ± 8 years), and the number of patients taking insulin (six of seven [86 percent] vs 11 of 13 [85 percent]) were similar between diabetics with and without an abnormal ejection fraction response to exercise, respectively.

**Discussion**

Left ventricular dysfunction previously has been demonstrated in young asymptomatic diabetics. In the present study where the exercise MUGA scan was used to estimate left ventricular performance, seven out of 20 diabetics (35 percent) decreased or failed to show an increase in their ejection fraction at peak exercise, whereas all but one age- and sex-matched control subjects had an increase in ejection fraction during exercise. Similar results were reported by Mildenberger et al and Vered et al. These results support the argument that subclinical left ventricular dysfunction is present in a significant number of diabetic patients. Although coronary artery disease cannot be excluded since none of the patients in the study had coronary angiography, the relatively young age of the diabetic patients, absence of ischemic ST segment changes during the stress ECG, and the absence of regional wall motion abnormalities on the MUGA scan make this unlikely.

The reason for altered left ventricular performance in diabetes has not been resolved. One possibility is that impaired glucose transport across the cell membrane may interfere with metabolic function of the myocardial cell, and thereby alter contractility. Animal studies have demonstrated that adequate glycemic control may reverse functional impairment of the myocardium. Clinical studies in humans have produced mixed results. On the one hand, it has been demonstrated that left ventricular dysfunction occurs above a threshold blood sugar of 180 mg/dl, and improvement of cardiac function is seen with close control of hyperglycemia in insulin-dependent diabetics. On the other hand, others have reported no relationship between the blood glucose level and LV performance. In the current study, we did not find a correlation between the fasting blood glucose level and LV performance. The mean fasting glucose level for group 1, in addition, was not significantly higher than that for group 2. We also did not find a meaningful correlation between the degree of diabetic control over a sustained period of time, as measured by the HbA1c level and LV performance. The reason that a correlation was not found may be due to the high number of patients who were found to have poorly controlled diabetes as determined by the HbA1c level. Inclusion of a larger number of well controlled diabetics would be more representative and perhaps produce a better linear correlation. Nevertheless, the HbA1c levels tended to be higher in diabetics with a poor response to exercise as compared to those with a normal response, even though this difference did not reach statistical significance.

Angiopathy of small coronary arteries may account for changes in LV function seen in diabetics. Our study neither confirms nor rejects small vessel involvement as the cause of exercise-induced LV dysfunction. However, we did not find a relationship between the duration of diabetes and the presence of LV dysfunc-
tion. In diabetics with abnormal LV function, the
duration of diabetes was 8 ± 7 years, while in those
with normal LV function the duration was 14 ± 8 years
(p<0.05). This is not consistent with epidemiologic
studies which have shown that the frequency and
severity of angiopathy is time dependent.4,19 In addi-
tion, there was a poor correlation between LV function
abnormalities and the presence of either retinal or
glomerular angiopathy. Three of seven patients (42
percent) in the subgroup of diabetics with LV dysfunc-
tion and six of 13 (46 percent) with normal LV function
had significant proteinuria and/or retinopathy. Our
data do not support the presence of generalized
microvascular involvement in diabetics with LV fun-
ction abnormalities.

This study measured the response of LV systolic
function during and after exercise. There was no
ttempt to evaluate diastolic function, which might be
a more sensitive index if the primary abnormality is
related to myocardial stiffness from deposition of
myocardial glycoprotein. The HbA1c levels might
better correlate, therefore, with LV diastolic dysfunc-
tion rather than systolic function. A further study
addressing this aspect of diabetes may be warranted
in view of the possibility that early detection of diabetic
abnormalities may be potentially reversible with bet-
ter diabetic control.

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Subclinical Left Ventricular Abnormalities (Arvan et al)