Two Years of Intensive Glycemic Control and Left Ventricular Function in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM)

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OBJECTIVE — The Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) was a multicenter randomized prospective study of 153 male type 2 diabetic patients to assess the ability to sustain clinically significant glycemic separation between intensive and standard treatment arms. A trend toward an excess of combined cardiovascular events in the intensive treatment arm of this trial was reported earlier. The present analysis was done to evaluate the effect of 2 years of intensive glycemic control on the left ventricular (LV) function.

RESEARCH DESIGN AND METHODS — The patients were randomized to intensive step treatment with insulin alone or with sulfonylurea (intensive treatment arm [INT], *n* = 75) or to standard once-daily insulin injection (standard treatment arm [STD], *n* = 78) treatment. A total of 136 patients (standard treatment arm [STD], *n* = 70; INT, *n* = 66) had radionuclide ventriculography at entry and at 24 months for the assessment of LV function.

RESULTS — There was no difference in the mean LV ejection fraction (at entry: STD 57.1 ± 9.51%; INT 58.1 ± 8.7%; at 24 months: STD 57.3 ± 10.8%, INT 59.5 ± 10.7%), peak filling rate (at entry: STD 2.6 ± 0.7 end diastolic volume per second, INT 2.4 ± 0.8 end diastolic volume per second; at 24 months: STD 2.7 ± 1.0 end diastolic volume per second, INT 2.5 ± 0.7 end diastolic volume per second), or time to peak filling rate (at entry: STD 195.3 ± 69.5 ms, INT 185.6 ± 62.4 ms; at 24 months: STD 182.6 ± 64.8 ms, INT 179.2 ± 61.2 ms) between the 2 treatment arms. A subgroup analysis of 104 patients (STD, *n* = 53; INT, *n* = 51) that omitted individuals with intervening cardiac events/revascularization or a change in cardioactive medications also showed no difference in the LV function at entry and at 24 months between the 2 groups. Abnormal LV ejection fraction at baseline predicted cardiac events (interval between cardiac beats [RR] = 2.5).

CONCLUSIONS — Two years of intensive glycemic control does not affect the LV systolic or diastolic function in patients with type 2 diabetes.

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Abbreviations: CSPCC, Human Rights Committee of the Cooperative Studies Program Coordinating Center; INT, intensive treatment arm; LV, left ventricle; LVEF, left ventricular ejection fraction; PFR, peak filling rate; RR, interval between cardiac beats; STD, standard treatment arm; TPFR, time to peak filling rate; VA CSDM, Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) was initiated in January 1990 at 5 Veterans Affairs medical centers. A total of 153 male veterans with type 2 diabetes were studied. The aim of the trial was to determine whether a statistically and clinically significant difference in HbA_{1c} could be safely achieved between the standard and the intensive treatment groups while maintaining HbA_{1c} levels in both groups within the range then acceptable in community practice. During the feasibility study, a variety of data were collected to evaluate various microvascular and macrovascular indicators of complications, safety of intensive therapy, and quality of life (1). There was a trend toward an excess of combined cardiovascular events in the intensive treatment arm of this trial, which included an excess of episodes of congestive heart failure (2).This article summarizes the effects of 2 years of intensive glycemic control on myocardial systolic and diastolic function.

RESEARCH DESIGN AND METHODS

This was a randomized prospective study with a mean follow-up of 27 months (range 18–35). The study protocol was approved by the Human Rights Committee of the Cooperative Studies Program Coordinating Center (CSPCC) in Hines, Illinois, and by similar committees of the participating centers.

Subjects

The details of the inclusion and exclusion criteria are given in a previous report (3). In brief, patients were excluded if they had conditions that would have precluded intensive treatment, end point evaluation, or continuance into a proposed long-term study. All the patients were either receiving insulin or were on a maximum dose of sulfonylurea with an HbA_{1c} at entry >3 SD above the mean of normal [5.05 ± 3 (0.5 SD) = 6.55%].

Randomization

The patients were stratified at entry by the 5 participating hospitals and the presence

Table 1—*Baseline characteristics of the select subgroup*

Characterictics	STD	INT	*P*
n	53	51	—
Age (years)	59.9 ± 6.3	60.5 ± 6.7	0.64
Duration of diabetes (years)	8.0 ± 4.2	7.9 ± 3.7	0.90
BMI (kg/m^2)	30.8 ± 5.2	30.6 ± 4.4	0.79
HbA_{1c} (%)	9.2 ± 1.4	9.3 ± 1.9	0.87
Insulin dose (U/day)	32.8 ± 19.0	30.6 ± 14.1	0.37
Total cholesterol (mg/dl)	211.3 ± 48.6	219.0 ± 60.8	0.47
LDL cholesterol (mg/dl)	137.5 ± 39.2	137.2 ± 57.0	0.97
HDL cholesterol (mg/dl)	42.1 ± 9.9	42.4 ± 11.1	0.90
Triglyceride (mg/dl)	174.6 ± 83.5	211.2 ± 172.2	0.17
Systolic blood pressure (mmHg)	134.3 ± 17.3	137.5 ± 16.0	0.32
Diastolic blood pressure (mmHg)	81.6 ± 7.9	81.3 ± 9.3	0.89
Plasma fibrinogen (g/l)	322.9 ± 92.3	325.7 ± 89.4	0.87
Lipoprotein(a) (g/l)	24.7 ± 22.7	31.3 ± 30.5	0.21
Prior known cardiovascular complications	18 (33.96)	20 (39.22)	0.68
Myocardial infarction	5 (9.4)	9 (17.6)	0.26
Angina and/or coronary artery disease	10 (18.9)	6 (11.8)	0.42
Congestive heart failure	3 (5.66)	0 (0)	0.24
Cerebral vascular accident	3 (5.66)	4 (7.89)	0.71
Transient ischemic attack	1 (1.89)	3 (5.88)	0.36
Intermittent claudication	7 (13.21)	7 (13.73)	1.0
Coronary artery bypass graft	0 (0)	1 (1.96)	0.56
Silent findings	47 (88.68)	40 (78.43)	0.19
Smoking status	46 (86.79)	42 (82.35)	0.27
Albuminuria (mg/dl)			
0–30	24 (45.28)	23 (45.10)	0.95
31–300	27 (50.94)	25 (49.02)	—
301–500	2 (3.77)	3 (5.88)	—

Data are means ± SD or *n* (%). Select subgroup indicates patients without intervening cardiac events or change in cardioactive medications. For prior known cardiovascular complications, some patients had multiple diagnoses. Silent findings include patients with prior known cardiovascular complications. Findings include abnormal resting or ambulatory electrocardiograms or radionuclide scan–detected LVEF <50%.

or absence (2 strata) of prior complications (myocardial infarction, angina pectoris, congestive heart failure, transient ischemic attack, or cerebrovascular accidents). Within these 10 strata, the patients were randomized to intensive glycemic control or standard treatment.

Treatment arms

The standard treatment arm (STD) (*n* = 78) received 1 injection of intermediate or long-acting insulin per day with the goal of avoiding excessive hyperglycemia and symptoms of glucosuria, ketonuria, and hypoglycemia. The HbA_{1c} in these patients could not exceed >2 SD above mean levels in the outpatient clinics of participating centers (12.9%, "alert value"). In the intensive treatment arm (INT) (*n* = 75), the aim was to reduce and maintain the HbA_{1c} level as close to normal (5.1 ± 1%) as possible. Details about the step management protocol for the intensive treatment group were reported earlier (3). Briefly, the 4 steps in this protocol were as follows:

1. Evening intermediate- or long-acting insulin only
2. Evening insulin with daytime glipizide
3. Insulin twice daily, no glipizide
4. More than 2 injections of insulin, no glipizide

Patients moved to a higher step only if the operational goals of target HbA_{1c} were not met.

Radionuclide ventriculography

Radionuclide ventriculography scans were done to assess the left ventricular (LV) systolic function, LV ejection fraction (LVEF) and diastolic function, peak filling rate (PFR), and time to peak filling rate (TPFR) at entry and at 24 months' follow-up. A standard procedure was followed at each of the 5 centers. Red blood cells were labeled in vivo with 20 mCi of 99 mTc pertechnetate. Images were obtained in the left anterior oblique projection with 10–20° caudal angulation at 5 min after the injection of 99 mTc pertechnetate. The aorta and other high-count structures were excluded from the background region of interest. Data collection was done with a 64 × 64 matrix with a minimum of 24 frames per cycle. A total of 200 kilocounts/frame or 200 counts/pixel were obtained from the center of the LV. The smallest interval between cardiac beats (RR) acceptance window for beat rejection that was consistent with reasonable scan time was used. The initial and follow-up scans were acquired and processed using the same imaging system for a given subject. The scans were read locally at the 5 centers using predetermined standards for interpretation, with periodic quality control by the nuclear medicine consultant and the CSPCC, and reported to the Data Monitoring Board. The LVEF was considered abnormal when reported as <50%. The change in the LVEF was considered to be significant if the LVEF changed by 10% (absolute value) from a baseline of <60% or changed by 15% (absolute value) from a baseline of ≥60%.

Statistical analysis

Comparisons of treatment arms on continuous variables were analyzed using Student's *t* tests. Discrete variables were analyzed with the χ^2 test. Examination of the relationship between cardiac events during follow-up and baseline characteristics began with calculations of crude incidence rate ratios. This was followed by estimates of survival using the Kaplan-Meier method. Survival was defined as the time from randomization to the occurrence of the first cardiac event. Finally, Cox regression was used to examine the influence of multiple variables simultaneously on survival free of cardiac events. Commercially available software (PHREG procedure in SAS; SAS Institute, Cary, NC) was used for the Cox analysis. A 2-tailed *P* value of ≤0.05 is considered to be statistically significant.

RESULTS — Of the 153 patients, 152 had radionuclide ventriculography scan at baseline (STD, *n* = 77; INT, *n* = 75), and 136 had repeat scans at 24 months. Of the other patients, 10 died and 4 discontinued the study; 3 did not complete the second test for miscellaneous reasons unrelated to the treatment assignment.

Table 2—*LV systolic and diastolic variables of the full cohort*

Variables	STD	INT	*P*
n	70	66	—
LVEF			
Baseline (%)	57.1 ± 9.5	58.1 ± 8.7	0.55
24 months (%)	57.3 ± 10.8	59.5 ± 10.7	0.25
Change over 24 months (%)	0.24 ± 8.6	1.4 ± 9.6	0.45
PFR			
Baseline (end diastolic vol/s)	2.6 ± 0.7	2.4 ± 0.8	0.26
24 months (end diastolic vol/s)	2.7 ± 1.0	2.5 ± 0.7	0.17
Change over 24 months (end-diastolic vol/s)	0.09 ± 0.98	0.04 ± 0.75	0.70
TPRF			
Baseline (ms)	195.3 ± 69.5	185.6 ± 62.4	0.39
24 months (ms)	182.6 ± 64.8	179.2 ± 61.2	0.75
Change over 24 months (ms)	−12.71 ± 69.88	−6.31 ± 82.81	0.63

Data are means ± SD unless otherwise indicated. *n* = 136.

We analyzed and compared the data from the full cohort of 136 patients who had 2 scans (STD, *n* = 70; INT, *n* = 66). In the second part of this evaluation, an analysis was performed in a subgroup of 104 patients (STD, *n* = 53; INT, *n* = 51). To better analyze whether or not glycemic control by itself had any effect on LV function, 32 patients were excluded from the second analysis for 2 reasons. First, patients who had a change in medications between the 2 scans that could affect LV function (calcium-channel blockers, ACE inhibitors, β-blockers, α-blockers, and digoxin) were excluded (STD, *n* = 8; INT, *n* = 9). Second, patients having significant interim cardiac events between the 2 scans (MI and/or angina and/or revascularization procedures) that could interfere with the ventricular function independently of treatment assignment were excluded (STD, *n* = 9; INT, *n* = 6). The resulting cohort will be referred to as the "select subgroup" of patients.

Baseline characteristics

The baseline characteristics of the whole cohort (*n* = 153) were reported earlier (1). The baseline characteristics of the select subgroup of patients are summarized in Table 1. There were no significant differences in the baseline characteristics of the whole cohort and those of either the full cohort that had 2 radionuclide ventriculography scans (*n* = 136), the select subgroup (*n* = 104), or the excluded patients (*n* = 32).

Glycemic control

The mean HbA_{1c} separation between the 2 treatment arms of the full cohort that had 2 scans (*n* = 136) (STD, 9.3%; INT, 6.9%) and of the select subgroup (*n* = 104) (STD, 9.1%, INT, 7.0%) was >2.0% ($P < 0.001$). The glycemic separation was achieved by 6 months and was maintained for the mean follow-up period of 27 months (range 18–35).

Full cohort

In the full cohort (*n* = 136), there was no correlation of the LV systolic or diastolic function with age, duration of diabetes, or history of insulin use at entry. Table 2 summarizes the LV function of the full cohort at entry and at 24 months.

The number of patients with abnormal LVEF (<50%) in the 2 treatment arms was similar at baseline and 24 months (baseline: STD = 13, INT = 9; 24 months: STD = 10, INT = 9). Similarly, the number of patients having an increase (STD = 9, INT = 14) or decrease (STD = 4, INT = 5) in LVEF was not significantly different in the 2 treatment groups at 24 months' follow-up. The numbers of patients with wall motion abnormality at baseline and at 24 months were not significantly different in the STD and INT treatment arms (baseline: STD = 20, INT = 16; 24 months: STD = 16, INT = 12).

Select subgroup analysis

In the group without any intervening cardiac events or a change in cardioactive medications (*n* = 104), the lipid profile was similar between the 2 treatment arms at 24 months. Total cholesterol was STD 198.3 ± 32.7 and INT 201.6 ± 40 mg/dl; LDL cholesterol was STD 125.8 ± 27.4 and INT 130.7 ± 35.6 mg/dl; HDL cholesterol was STD 39.3 ± 9.9 and INT 40.5 ± 11.1 mg/dl; and triglycerides were STD 166.7 ± 95.2 and INT 163.4 ± 114.4 mg/dl. The smoking status was also similar in the 2 treatment arms at 24 months (48 STD patients, 40 INT patients). The daily insulin dose at 24 months was significantly higher in the INT arm than in the STD arm (STD 59.4 ± 39.2 U, INT 103.9 ± 76.1 U, $P < 0.01$).

As seen in Table 3, LV function was similar in the 2 treatment arms at baseline and at 24 months. The number of patients having abnormal LVEF at baseline and at 24 months' follow-up was similar in the 2 treatment arms (baseline: STD = 10, INT = 7; 24 months: STD = 9, INT = 8). There was no difference in the number of patients having an increase (STD = 8, INT = 9) or decrease (STD = 4, INT = 2) in LVEF over the 24-month follow-up period in the 2 groups. The number of patients having wall motion abnormality in the STD and the

Table 3—*LV systolic and diastolic variables of the select subgroup*

Variables	STD	INT	*P*
n	53	51	—
LVEF			
Baseline (%)	57.6 ± 9.6	58.3 ± 8.1	0.71
24 months (%)	58.0 ± 10.8	59.7 ± 10.1	0.39
Change over 24 months (%)	0.40 ± 9.5	1.4 ± 9.3	0.55
PFR			
Baseline (end diastolic vol/s)	2.6 ± 0.7	2.5 ± 0.8	0.50
24 months (end diastolic vol/s)	2.7 ± 1.1	2.5 ± 0.7	0.29
Change over 24 months (end diastolic vol/s)	0.12 ± 1.08	0.03 ± 0.79	0.62
TPRF			
Baseline (ms)	184.4 ± 60.4	191.6 ± 65.5	0.61
24 months (ms)	198.7 ± 74.4	184.9 ± 63.9	0.97
Change over 24 months (ms)	−14.28 ± 72.28	−6.72 ± 90.85	0.64

Data are means ± SD unless otherwise indicated. *n* = 104.

INT arm was similar at baseline and at 24 months (baseline: STD = 16, INT = 11; 24 months: STD = 13, INT = 11).

Baseline systolic function and late cardiovascular events

Of the 152 patients who had baseline evaluation of LV function, 26 (33.77%) patients in the STD and 31 (41.33%) patients in the INT group had a history of prior cardiovascular events. Nineteen patients in the STD arm and 13 patients in the INT arm had abnormal LVEF at baseline. In the full trial, 40 patients (STD = 16, INT = 24) had 61 new cardiovascular events (STD = 26; INT = 35) during the study. Of these new cardiovascular events, 15 patients in the STD arm and 23 patients in the INT arm had new heart events (defined as angina, myocardial infarction, congestive heart failure, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty). As reported earlier, history of a clinical cardiovascular event was a predictor of a postrandomization cardiovascular event that approached statistical significance ($P = 0.06$). The next best predictors of postrandomization cardiovascular events were a lower HbA_{1c} before the event ($P = 0.1$) and assignment to INT ($P = 0.12$) (2). Of the silent abnormalities at baseline (12-lead electrocardiogram, ambulatory electrocardiogram, and radionuclide ventriculography scan), abnormal LVEF at baseline was the only parameter that predicted future cardiac and total cardiovascular events. In the current analysis, abnormal LVEF at baseline predicted future cardiac events (RR = 2.5, $P = 0.0189$). History of prior cardiac events was the strongest predictor of future cardiac events (RR = 3.7, $P = 0.0009$). History of total prior cardiovascular events (cardiac and peripheral vascular) predicted future cardiac events with a RR of 2.5 ($P = 0.01$). When history of prior cardiac events and abnormal LVEF at baseline were combined, there was no gain in the predictive value.

CONCLUSIONS — The incidence and prevalence of cardiac disease is reported to be significantly higher in patients with type 2 diabetes than in those without diabetes (4–7). Patients with diabetes have a higher prevalence of myocardial dysfunction in the absence of coronary artery disease, often attributed to a specific "diabetic cardiomyopathy" (5). Various pathophysiological mechanisms have been postulated as responsible for diabetic cardiomyopathy (8–12).

The present study is the largest and longest prospective examination of the relationship of glycemic control and cardiac function.

Cardiac systolic function was noted to be similar in the 2 treatment arms of the present study at baseline and after 24 months. Thus, LV systolic function was not affected by differences in intensity of glycemic control.

Although animal studies have demonstrated a beneficial effect of improved glycemic control on myocardial function (8,13), studies in humans have not been consistent (14–17). There was no difference in the systolic function as studied by radionuclide ventriculography between 8 patients with type 1 diabetes and 11 control subjects (15). Decreased cardiac output was reported in 23 patients with type 2 diabetes as compared with 22 control subjects and 16 patients with type 1 diabetes (17). Increased ratio of the pre-ejection period to LV ejection time and decreased fractional shortening has been noted in patients with diabetes (16,18). In studies by Cerasola et al. (16) and Vered et al. (19), the postexercise LV systolic function was impaired in patients during poor glycemic control and improved with lower blood glucose levels.

Cardiac diastolic function in the present study as measured by PFR and TPFR was not different between the 2 arms at baseline and at 24 months. The literature suggests that the diastolic function in our patients was borderline abnormal for both PFR (normal >2.5) and TPFR (normal <180) at entry and at 24 months' follow-up (20,21). This result might indicate a subtle diastolic LV dysfunction in these subjects, which did not change over 2 years, irrespective of the treatment assignment.

In other studies, the PFR and TPFR were abnormal in patients with type 1 and type 2 diabetes compared with normal control subjects (15,17). Prolonged isovolumic relaxation period and delayed mitral valve opening in patients with type 1 and type 2 diabetes compared with normal subjects has been demonstrated (18,22). The impairment of diastolic function is noted to be more pronounced in patients with type 2 diabetes than in those with type 1 diabetes (17,18). Lerman et al. (14) found no significant change in the LV diastolic function after 4 weeks of intensive glycemic control with insulin therapy in 8 type 1 diabetic patients.

A trend toward excess combined cardiovascular events in the intensive treatment arm of this trial, including excess episodes of congestive heart failure, was reported earlier (2). However, as reported here, there were no deleterious effects of intensive glycemic control on LV function. The study had a 99% power to detect a drop of LVEF to $<50\%$ — a recognized clinically important change.

In conclusion, 2 years of strict glycemic control did not affect the LV function. We acknowledge that the effects of glycemic control on macrovascular complications may be delayed and it is possible that had the study been continued longer, an effect might have been seen. The long-term effects of glycemic control on the cardiovascular complications of type 2 diabetes is the subject of a Veterans Affairs diabetes cooperative trial, which is at inception as of this writing.

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References

1. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel N, Comstock JP, Emanuele NV, Levin SR, Henderson W, Lee HS, VACSDM Study Group: VA Cooperative Study on Glycemic Control and Complications in Type II Diabetes: results of the feasibility trial. *Diabetes Care* 18:1113–1123, 1995
2. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS, VACSDM Study Group: Cardiovascular events and correlates in the Veterans Affairs diabetes feasibility trial. *Arch Intern Med* 157:181–188, 1997
3. Abraira C, Emanuele N, Colwell J, Henderson W, Comstock J, Levin S, Nuttall F, Sawin C, VACSDM Study Group: Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 15:1560–1571, 1992
4. Geiss LS, Herman WH, Smith PJ: Mortality in non-insulin-dependent diabetes. In *Diabetes in America*. 2nd ed. Harris M, Ed. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and

Digestive and Kidney Diseases, 1995, p. 233–255 (NIH publ. no. 95-1468)
5. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2035–2038, 1979
6. Ford ES, DeStefano F: Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. *Am J Epidemiol* 133:1220–1230, 1991
7. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
8. Popovich BK, Boheler KR, Dillmann WH: Diabetes decreases creatine kinase enzyme activity and mRNA level in the rat heart. *Am J Physiol* 257:573–577, 1989
9. Heyliger CE, Prakash A, McNeill JH: Alterations in cardiac sarcolemmal Ca^{2+} pump activity during diabetes mellitus. *Am J Physiol* 252:540–544, 1987
10. Eto M, Watanabe K, Sekiguchi M, Iwashima Y, Morikawa A, Oshima E, Ishii K: Metabolic and morphological changes of the heart in Chinese hamsters (CHAD strain) with spontaneous long-term diabetes. *Diabetes Res Clin Pract* 3:297–305, 1987
11. Zola B, Kahn JK, Juni JE, Vinik AI: Abnormal cardiac function in diabetic patients with autonomic neuropathy in the absence of ischemic heart disease. *J Clin Endocrinol Metab* 63:208–214, 1986
12. Dhalla NS, Pierce GN, Innes IR, Beamish RE: Pathogenesis of cardiac dysfunction in diabetes mellitus. *Can J Cardiol* 1:263–281, 1985
13. Fein FS, Miller-Green B, Zola B, Sonnenblick EH: Reversibility of diabetic cardiomyopathy with insulin in rabbits. *Am J Physiol* 250:108–113, 1986
14. Lerman IG, Marquez-Murillo MF, Lopez-Alvaranga JC, Malagon J, Osequera J, Ponce de Leon S, Sanchez-U T, Fernandez M, Gomez-Perez FJ: Effect of major improvement in glycemic control on results of cardiovascular function tests in patients with insulin dependent diabetes mellitus. *Endocrin Pract* 4:76–81, 1998
15. Ruddy TD, Shumak SL, Liu PP, Barnie A, Seawright SJ, McLaughlin PR: The relationship of cardiac diastolic dysfunction to concurrent hormonal and metabolic status in type 1 diabetes mellitus. *J Clin Endocrinol Metab* 66:113–118, 1988
16. Cerasola G, Donatelli M, Cottone S, D'Ignoto G, Grasso L, Morici ML, Terrizzi C, Verga S, Bompiani GD: Effects of dynamic exercise and metabolic control on left ventricular performance in insulin-dependent diabetes mellitus. *Acta Diabetologica Latina* 24:263–270, 1987
17. Ferraro S, Filardi-Perrone P, Maddalena G, Desiderio A, Gravina E, Turco S, Chiariello M: Comparison of left ventricular function in insulin and non-insulin dependent diabetes mellitus. *Am J Cardiol* 71:409–414, 1993
18. Uusitupa M, Mustonen J, Laakso M, Vainio P, Lansimies E, Talwar S, Pyorala K: Impairment of diastolic function in middle aged type 1 and type 2 diabetic patients free of cardiovascular disease. *Diabetologia* 31: 783–791, 1988
19. Vered Z, Battler A, Segal P, Liberman D, Yerushalmi Y, Berezin M, Neufeld H: Exercise induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus. *Am J Cardiol* 54:633–637, 1984
20. Bacharach SI, Green MV, Borer JS, Hyde JF, Farkas SP, Johnson GS: Left ventricular peak ejection rate, filling rate, and ejection fraction-frame rate requirements at rest and exercise: concise communication. *J Nucl Med* 20:189–193, 1979
21. Mancini GBJ, Slutsky RA, Norris SL, Bhargava V, Ashburn WI, Higgins CB: Radionuclide analysis of peak filling rate, filling fraction, and time to peak filling rate. *Am J Cardiol* 51:43–51, 1983
22. Sanderson JE, Brown DJ, Rivellese A, Kohner E: Diabetic cardiomyopathy? An echocardiographic study of young diabetics. *BMJ* 1:404–407, 1978