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Myocardial Mechanics in Young Adult Patients With Diabetes Mellitus: Effects of Altered Load, Inotropic State and Dynamic Exercise

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The disease entity "diabetic cardiomyopathy" has been extensively described in young patients with diabetes in the absence of ischemic, hypertensive or valvular heart disease. The most convincing data have been a 30% to 40% incidence of decreased radionuclide angiographic left ventricular ejection fraction response to dynamic exercise. In the current study, the hypothesis was tested that this abnormal ejection fraction response was due to alterations in ventricular loading conditions or cardiac autonomic innervation (extrinsic factors), or both, rather than to abnormalities in intrinsic ventricular systolic fiber function (contractility).

Twenty normotensive patients with diabetes (mean age 30 ± 5 years, mean duration 15 ± 6 years) and 20 age-matched normal subjects were studied. All patients with diabetes had a normal treadmill exercise tolerance test without evidence of myocardial ischemia. By radionuclide angiography, all normal subjects increased ejection fraction with exercise (62 ± 4% to 69 ± 6%; $p < 0.001$). In contrast, 11 (55%) of 20 patients with diabetes maintained or increased ejection fraction with exercise (group 1; 62 ± 4% to 69 ± 6%; $p < 0.001$) and 9 (45%) of 20 showed an exercise-induced decrease (group 2; 73 ± 4% to 66 ± 6%; $p < 0.001$). No difference in the incidence of microangiopathy, as noted by funduscopic examination, was present between the diabetic groups. Despite the abnormal ejection fraction response to exercise in the group 2 patients with diabetes, all patients with diabetes had a normal response to afterload manipulation, normal baseline ventricular contractility as assessed by load- and heart rate-independent end-systolic indexes and normal contractile reserve as assessed with dobutamine challenge.

Autonomic dysfunction did not explain the disparate results between the group 2 patients' radionuclide angiographic data and their load-independent tests of ventricular contractility and reserve. In addition, the high ejection fraction at rest in group 2 patients (73 ± 4% versus 62 ± 4% for normal subjects; $p < 0.001$) was not related to the abnormal tests of autonomic function. Thus, when left ventricular systolic performance was assessed by load- and rate-independent indexes, there was no evidence for cardiomyopathy in young adult patients with diabetes who have normal blood pressure and no ischemic heart disease.

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Prior studies (1–10) have suggested that left ventricular contractility is abnormal in a high percentage of young patients with diabetes in the absence of ischemic, hypertensive or valvular heart disease. One of the most widely used clinical methods for assessing cardiac performance in these patients has been the left ventricular ejection fraction response to exercise as determined by radionuclide angiography. This test has been reported (8,9) to be abnormal in more than one third of such patients, suggesting that ventricular systolic dysfunction is present in a large subset of young adult patients with diabetes. On the basis of these and other studies, the clinical entity of diabetic cardiomyopathy appears to have been well established (1–10). However, more detailed analysis has raised a major question regarding the physiologic limitations of the diagnostic methods on which these conclusions are based.

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The most important problem deals with the widespread use of traditional ejection phase indexes of ventricular performance, which are unable to distinguish abnormalities in ventricular contractility from derangements in preload, afterload and heart rate (11–14). This issue is further complicated by attempts to use the ejection fraction response to dynamic exercise as a measurement of contractile reserve (12). Meaningful interpretation of this response is confounded by the associated acute circulatory adjustments that accompany dynamic exercise. These include peripheral vasodilation in exercising muscles, neurally mediated changes in cardiac parasympathetic and sympathetic tone, the release of catecholamines from the adrenal medulla and alterations in systemic venous capacitance leading to augmentation of venous return and maintenance of ventricular preload (11,12). Derangement of *any one* of these mechanisms could result in failure to increase ejection fraction without invoking a concomitant depression in contractile reserve.

Thus, overall cardiac performance in response to exercise may be blunted independent of the level of ventricular contractility. For these reasons, it is conceivable that alterations in loading conditions or cardiac autonomic innervation, or both, rather than abnormalities in contractility are responsible for the nonischemic "cardiomyopathy" previously described in young patients with diabetes. To investigate this possibility, we studied a group of young (<40 years) patients with long-standing diabetes and no clinical evidence of hypertensive, valvular or ischemic heart disease, who were representative of the patient population in which a diabetic cardiomyopathy has been reported previously (8,9).

Methods

Study patients. These consisted of 20 patients with type 1 diabetes (11 men and 9 women ranging in age from 20 to 39 years [mean ± SD 30 ± 5]). All had been insulin dependent for >5 years (mean 15 ± 6), were taking no cardioactive medications and had a funduscopic examination performed within the prior year specifically for evidence of retinal microangiopathy. None had clinical or cardiac ultrasound evidence for coronary artery disease, valvular heart disease or systemic hypertension. All performed a treadmill exercise test that was negative for myocardial ischemia as well as an exercise radionuclide angiographic study in which a peak rate-pressure product >23,000 was achieved with a heart rate >85% of the maximally predicted value for age and no exercise-induced regional wall motion abnormalities. Data acquired from the patients with diabetes were compared with those obtained from 20 normal subjects matched for gender and age (mean 30 ± 6 years). Half of these normal subjects underwent radionuclide angiographic evaluation and the remainder underwent pharmacologic challenges during echocardiographic imaging. These studies were approved by the Institutional Review Board of the University of Chicago Medical Center. In all cases, informed written consent was obtained.

Experimental Design

Radionuclide angiographic data. First pass radionuclide angiography was performed with the patient in the upright position at rest and during exercise. Images were acquired from the anterior projection using a multicrystal gamma camera (Baird-Atomic System-77) equipped with a 1 in. (2.54 cm) parallel-hole collimator. Fifteen to eighteen millicuries (mCi) of technetium-99m-diethylene-triamine penta-acetic acid was injected for the rest measurement and 20 to 23 mCi was injected for exercise measurements. Specific details of this technique have been described elsewhere (15,16). After completion of the rest radionuclide study, exercise was performed on a bicycle ergometer (Fitron). Electrocardiographic monitoring of heart rate and rhythm was performed during rest and exercise studies. Blood pressure was recorded by cuff manometer at 2 min intervals during and after exercise until stable. All patients began exercise at a work load of 200 kp-m/min; the work load was then increased by 100 kp-m/min every minute. Criteria for an adequate exercise test were as noted above.

Echocardiographic data. The patients with diabetes and normal subjects were studied in the supine position using simultaneous recordings of two-dimensionally targeted M-mode echocardiograms of the left ventricle, phonocardiogram, electrocardiogram (ECG), indirect carotid pulse tracings and blood pressure measurements. Control subjects were premedicated with atropine (0.010 to 0.015 mg/kg) to depress vagal tone and allow baseline data to be acquired at heart rates comparable to the increased heart rates at rest found in the patients with diabetes. To assess baseline contractility over a wide range of ventricular loading conditions, recordings were made before and during infusion of the alpha-1 adrenoceptor agonist methoxamine (1 mg/min). This drug has no direct cardiac effect in the doses used in the current study (17). Recordings were obtained every 1 to 2 min until peak systolic pressure had increased 30 to 60 mm Hg above baseline at which time the methoxamine infusion was discontinued. The peak pressor effect lasted 2 to 5 min. Only data acquired within a 10 beat/min heart rate range were analyzed. When systemic arterial pressure had returned to within 5% of the initial value, an infusion of dobutamine hydrochloride (5 μg/kg per min) was begun. After 7 min, data collections were repeated.

Tests of cardiovascular autonomic nerve function. Two standard tests were selected to measure cardiac and extracardiac autonomic nerve function. The first test measured respirophasic variability in cardiac cycle length on ECG (18–23). Data were acquired with the patient resting in the supine position and taking six deep breaths per minute. This

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respiratory rate was chosen because it results in the maximal respiratory variation in heart rate (19). An expiration/inspiration (E/I) ratio was obtained for each breath cycle by dividing the longest RR interval after expiration by the shortest after inspiration. A mean ratio was derived from the six breath cycles recorded over 1 min. This test is predominantly a measure of cardiac parasympathetic integrity (18,19). The second test measured the change in diastolic blood pressure due to sustained muscular exercise associated with isometric handgrip exercise (19). A handgrip dynamometer was maintained at 30% of maximal voluntary contraction for 5 min. Blood pressure was measured every 30 s using the Dinamap 1846SXP Vital Signs Monitor. The difference between the diastolic blood pressure obtained just before release and just before the onset of handgrip was taken as the measure of response. This test largely reflects extracardiac sympathetic nerve function.

Total glycosylated hemoglobin levels. These were measured by affinity chromatography (Isolab) as percentage of total hemoglobin and reflect the degree of blood glucose control for the previous 8 to 10 weeks.

Data Analysis

Radionuclide angiographic data. Radionuclide data were processed using the commercially available computer and software of the Baird System-77. This was performed after correction for detector nonuniformity, electronic dead time count loss of the instrument and for background measured just before injection. A time-activity curve was generated from a region of interest drawn over the left ventricle. This curve was used to identify the time of end-systole and end-diastole for individual beats. Sequential addition of data from 3 to 10 beats starting at end-diastole produced a representative cardiac cycle. Ejection fraction was calculated from the background-corrected representative cycle in the usual manner. Regional left ventricular function was assessed by analysis of wall motion using both the cinematic display of the representative cycle and the static display of a regional ejection fraction image.

Patients with diabetes were stratified into two groups according to their left ventricular ejection fraction response to exercise. If ejection fraction remained unchanged or increased, patients were placed in group 1. If ejection fraction decreased, patients were placed in group 2. This separation criterion was chosen to establish an ejection fraction response to exercise that would be considered abnormal by most investigators. The results from the patients with diabetes were compared with data obtained from the 10 normal subjects who underwent radionuclide angiographic evaluation.

Echocardiographic data. Left ventricular end-systolic and end-diastolic dimensions (D_{es}, D_{ed}) and wall thicknesses (h_{es}, h_{ed}) were measured from two-dimensionally targeted M-mode echocardiographic recordings, as described previously (24). Measurements were determined as the mean value of five cardiac cycles. Left ventricular percent fractional shortening (%ΔD) was calculated in the usual manner and ventricular ejection time (ET) was measured from the carotid pulse tracing. The rate-corrected mean velocity of left ventricular fiber shortening (Vcf_c) was calculated as (24)

$$Vcf_c = \frac{(\%\Delta D)}{\frac{ET}{\sqrt{RR}}} = \frac{\%\Delta D}{ET_c},$$

where RR is the interval between adjacent R waves on the ECG and ET_c is the ejection time corrected for heart rate.

Calibration of the carotid pulse tracings was performed with assignment of systolic blood pressure to the peak and diastolic blood pressure to the nadir of the tracing (25). Linear interpolation to the level of the incisura was then performed to estimate end-systolic pressure.

The left ventricular end-systolic meridional wall stress (σ_{es}, g/cm^2) was calculated by an angiographically validated method (26):

$$\sigma_{es} = (0.337)\frac{(P_{es})(D_{es})}{(h_{es})\left[1 + \frac{h_{es}}{D_{es}}\right]},$$

where P_{es} is end-systolic pressure (mm Hg), D_{es} and h_{es} are end-systolic dimension and wall thickness (cm), respectively, and 0.337 is a conversion factor. Data from patients with diabetes were compared with those obtained from the 10 normal subjects who underwent pharmacologic challenge.

The relation between left ventricular end-systolic wall stress and rate-corrected velocity of fiber shortening was used as a preload and heart rate-independent index of contractility that incorporates afterload into its analysis (24,27). This index has been used clinically to assess a wide array of subjects ranging from normal subjects to patients considered to be at risk for left ventricular contractile abnormalities (28–34).

Tests of cardiovascular autonomic nerve function. As reported previously, an expiration/inspiration ratio less than 1.10 is considered indicative of total or near total loss of parasympathetic influence on heart rate and a ratio between 1.10 and 1.15 is considered in the borderline range suggesting partial parasympathetic denervation of the heart (18–20). Because the ratio normally declines with increasing age, normal values adjusted for age were used in this study (21,22). The normal change in diastolic blood pressure in response to handgrip is an increase ≥16 mm Hg; an increase ≤10 mm Hg is abnormal (19). Changes of 11 to 15 mm Hg are considered in the borderline range (19).

Statistical analysis. Each subject served as his own control. The paired *t* test was used to assess the hemodynamic

Table 1. Summary of Radionuclide Angiographic Data Obtained in the Upright Position

	Normal Subjects (n = 10)	Group 1 (n = 11)	Group 2 (n = 9)
Hemodynamics			
Rest condition			
Heart rate (beats/min)	75 ± 10	81 ± 14	93 ± 11*†
Peak systolic pressure (mm Hg)	106 ± 13	111 ± 15	113 ± 16
Diastolic pressure (mm Hg)	67 ± 11	76 ± 9	69 ± 9
Peak exercise			
Heart rate (beats/min)	168 ± 12	155 ± 14	160 ± 13
Peak systolic pressure (mm Hg)	166 ± 26	172 ± 26	180 ± 23
Peak rate-pressure product ($\times 10^3$)	27.9 ± 5.0	26.2 ± 2.2	28.7 ± 3.9
Left ventricular ejection fraction (%)			
Rest condition	61 ± 6	62 ± 4	73 ± 4*‡
Peak exercise	69 ± 6§	69 ± 6§	66 ± 6§
Change	8 ± 4	7 ± 4	−7 ± 7*‡

*$p < 0.001$, normal subjects versus group 2; †$p < 0.017$, group 1 versus group 2; ‡$p < 0.001$, group 1 versus group 2; §$p < 0.001$, exercise versus rest ejection fraction. Groups 1 and 2 indicate patients without and with, respectively, a decrease in ejection fraction during exercise.

changes induced by exercise and dobutamine relative to control values with a p value <0.05 considered statistically significant. Intergroup comparisons were performed with an unpaired *t* test that was corrected by using a Bonferonni factor for multiple comparisons whereby significance was accepted as $p < 0.05/k$, where k = number of comparisons. Group data are expressed as mean values ± SD.

The rate-corrected velocity of shortening versus end-systolic wall stress relation was assessed over a wide range of afterloads generated by methoxamine and during augmented contractility induced by dobutamine. As previously reported (35), our intraobserver coefficients of variation for Vcf_c and σ_{es} are 3.9% and 3.8% and interobserver coefficients of variation are 7.3% and 7.6%, respectively. Individual σ_{es}-Vcf_c lines were generated under baseline contractility conditions from a minimum of four data points using simple linear regression (least squares method). Intergroup comparisons were made using Vcf_c values obtained at a common level of left ventricular afterload (σ_{es} = 50 g/cm^2). This level of σ_{es} was chosen for comparisons because it approximated the mean baseline σ_{es} for the normal subjects in this and other studies (28,30,33).

Results

Response to dynamic exercise. Table 1 summarizes the hemodynamic and ejection fraction data acquired at the time of radionuclide angiographic imaging. All data were acquired with the subjects in the upright position. Under rest conditions, there were no intergroup differences for aortic peak systolic or diastolic pressure. Heart rate was higher for the group 2 patients with diabetes than for the normal subjects or group 1 patients. There were no intergroup differences at peak exercise for heart rate, systolic blood pressure or maximal rate-pressure product. No patient with diabetes demonstrated left ventricular regional wall motion abnormalities suggestive of myocardial ischemia at rest or peak exercise. Left ventricular ejection fraction increased in every normal subject from 61 ± 6% at rest to 69 ± 6% during peak exercise ($p < 0.001$) with a mean increase of 8 ± 4%

Figure 1. Left ventricular ejection fraction (%) obtained under rest conditions and at peak exercise (EX) for all study groups. With exercise, ejection fractions increased in normal subjects and group 1 patients and decreased in group 2 patients. Although ejection fraction was higher at rest for group 2, no intergroup differences in exercise ejection fraction values were present.

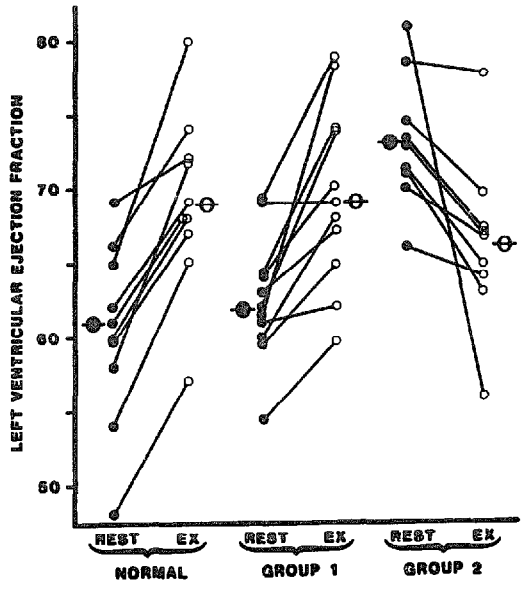


Table 2. Summary of Echocardiographic Data

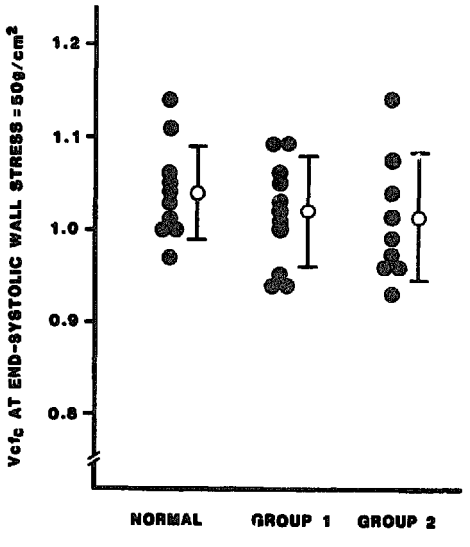
	Normal Subjects (n = 10)		Group 1 (n = 11)		Group 2 (n = 9)	
	Control	Dobutamine	Control	Dobutamine	Control	Dobutamine
Heart rate (beats/min)	82 ± 12	94 ± 11†	79 ± 10	95 ± 9†	81 ± 9	96 ± 17†
P_{ps} (mm Hg)	127 ± 11	150 ± 18†	123 ± 19	165 ± 23†	121 ± 17	158 ± 17†
P_d (mm Hg)	69 ± 7	81 ± 13*	71 ± 9	82 ± 11†	70 ± 13	82 ± 9*
P_{es} (mm Hg)	93 ± 7	113 ± 16†	92 ± 12	117 ± 27†	89 ± 16	104 ± 16*
D_{ed} (cm)	4.86 ± 0.29	4.77 ± 0.36	4.54 ± 0.39	4.47 ± 0.44	4.44 ± 0.39‡	4.34 ± 0.47
D_{es} (cm)	3.25 ± 0.28	2.82 ± 0.22†	2.95 ± 0.33	2.56 ± 0.28†	2.90 ± 0.28‡	2.47 ± 0.27†
h_{ed}	1.01 ± 0.10	1.01 ± 0.12	0.98 ± 0.12	0.99 ± 0.12	0.98 ± 0.11	0.98 ± 0.13
h_{es}	1.47 ± 0.12	1.70 ± 0.12†	1.50 ± 0.20	1.70 ± 0.20†	1.44 ± 0.19	1.63 ± 0.20†
ET_c	320 ± 12	306 ± 13†	331 ± 19	320 ± 20	332 ± 18	316 ± 21*
%ΔD	33.1 ± 2.5	41.3 ± 1.5†	34.9 ± 3.4	42.6 ± 2.7†	34.7 ± 2.6	43.0 ± 1.5†
Vcf_c	1.04 ± 0.07	1.35 ± 0.07†	1.06 ± 0.10	1.33 ± 0.07†	1.05 ± 0.11	1.36 ± 0.08†
σ_{es}	49 ± 8	40 ± 9†	42 ± 13	35 ± 7*	41 ± 13	33 ± 8

*$p < 0.05$ versus control; †$p < 0.01$ versus control; ‡$p < 0.017$; normal control versus group 2 control; D_{ed} = left ventricular end-diastolic dimension; σ_{es} = left ventricular end-systolic wall stress (g/cm²); D_{es} = left ventricular end-systolic dimension; ET_c = rate-corrected ejection time (s); h_{ed} = left ventricular end-diastolic wall thickness (cm); h_{es} = left ventricular end-systolic wall thickness (cm); %ΔD = left ventricular percent fractional shortening; P_d = aortic diastolic pressure; P_{es} = end-systolic pressure; P_{ps} = aortic peak systolic pressure; Vcf_c = rate-corrected velocity of shortening (circ/s).

units (Fig. 1). With exercise, ejection fraction was maintained or increased in 11 patients with diabetes (62 ± 4% to 69 ± 6%; $p < 0.001$). These patients, designated group 1, showed a mean ejection fraction change of 7 ± 4% units. Their response was indistinguishable from the response in normal subjects. In contrast, the nine patients with diabetes in group 2 showed a marked exercise-induced reduction in ejection fraction (73 ± 4% to 66 ± 6%; $p < 0.001$). This abnormal response occurred in 45% of our cohort of patients with diabetes. Importantly, the 7 ± 7% unit decline in ejection fraction that occurred in the group 2 patients was from a rest value of 73%. When compared with the rest ejection fraction for the normal subjects and group 1 patients with diabetes, the group 2 patients had much higher rest values ($p < 0.001$ versus normal subjects and group 1). In fact, none of the normal subjects or group 1 patients had a rest ejection fraction >69%, whereas eight of nine group 2 patients with diabetes had rest values >70%. Despite these differences, the exercise ejection fraction values for the normal subjects and group 1 and group 2 patients with diabetes were similar (69 ± 6%, 69 ± 6% and 66 ± 6%, respectively).

Baseline left ventricular contractility and response to afterload challenge (Table 2). With the study subjects in the supine position at the time of echocardiographic evaluation, there were no differences between the groups for baseline heart rate, systemic arterial pressure, left ventricular wall thickness, rate-corrected ejection time, overall ventricular performance (that is, percent fractional shortening or rate-corrected velocity of fiber shortening) or ventricular afterload (end-systolic wall stress). No significant differences existed between the groups of patients with diabetes for end-systolic and end-diastolic dimensions. When contractility was determined using the σ_{es}-Vcf_c relation generated over a wide range of afterloads, no differences between the normal subjects and group 1 and group 2 patients were evident. In all cases, the σ_{es}-Vcf_c values fell within the previously reported 95% confidence limits for normal contractility (24). There were no differences between groups in the mean values for the slope of the σ_{es}-Vcf_c relations. Ventricular contractility was further quantified as the rate-corrected Vcf at a common level of fiber load, thereby eliminating afterload as a confounding variable (Fig. 2). There were no intergroup differences in Vcf_c at an end-systolic wall stress of 50 g/cm². Thus, baseline contractility

Figure 2. Values for rate-corrected velocity of fiber shortening (Vcf_c) obtained at a common end-systolic wall stress of 50 g/cm². There were no differences between the normal and diabetic groups for baseline left ventricular contractility.



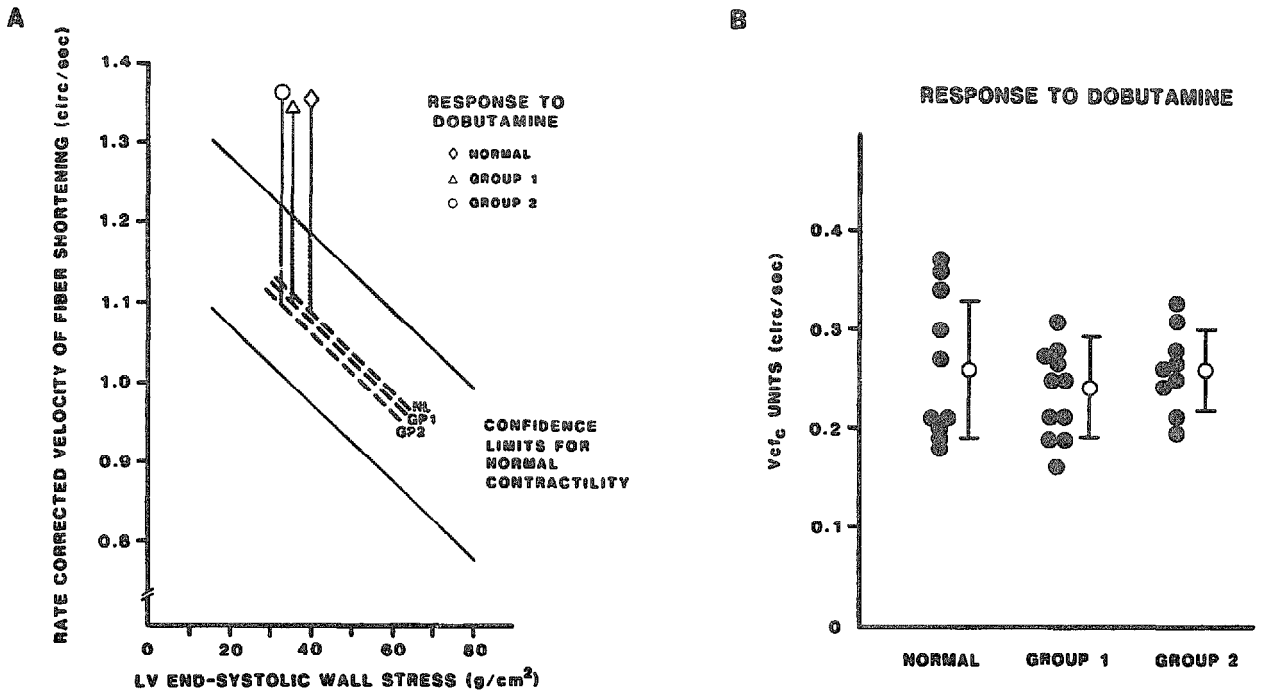


Figure 3. Assessment of left ventricular (LV) contractile reserve as assessed by dobutamine infusion. No intergroup differences were noted. See text for detailed explanation. Vcf_c = rate-corrected velocity of fiber shortening.

was normal in all of the patients with diabetes regardless of the ejection fraction response to upright dynamic exercise.

Response to pharmacologic challenge with dobutamine (assessment of left ventricular contractile reserve). The hemodynamic responses to dobutamine were the same for the normal subjects and both diabetic groups. Specifically, there were 1) similar increases in heart rate, systemic arterial pressures and left ventricular end-systolic wall thickness, 2) no change in left ventricular end-diastolic dimension and wall thickness, and 3) a decrease in left ventricular end-systolic dimension and wall stress. The net result was a highly significant increase in overall ventricular performance. Assessment of the importance of afterload reduction and augmented contractility to the improvement in rate-corrected velocity of fiber shortening is shown in Figure 3. Panel A shows a plot of σ_{es} versus Vcf_c with the shaded area representing the 95% confidence limits for normal contractility. The dashed lines are the mean regression data generated by afterload challenge during baseline contractility conditions for each study group. In all cases, dobutamine shifted the σ_{es}-Vcf_c relation above the 95% confidence limits in a manner characteristic of a positive inotropic effect (24,28,32,34). For each subject, the Vcf_c values at baseline and during dobutamine challenge were measured at the σ_{es} obtained during the dobutamine infusion. The contractile response was then quantified as the vertical deviation above the afterload challenge line (difference in Vcf_c values). Figure 3B demonstrates that dobutamine augmented left ventricular contractility to the same degree in normal subjects (0.26 ± 0.07), group 1 patients with diabetes (0.24 ± 0.05) and group 2 patients with diabetes (0.26 ± 0.04).

Cardiovascular autonomic nerve function. In both diabetic groups, a wide range of cardiovascular autonomic responses was present and the majority of patients had a normal response. Eight patients (four in each group) had unequivocal clinical features of autonomic dysfunction, that included at least two of the following: gastroparesis, diarrhea, gustatory sweating, impotence and orthostatic hypotension. In these patients, the expiration/inspiration ratio was either subnormal (three in each group) or in the borderline range (one in each group), whereas in all other patients it was within the normal range (Fig. 4). Diastolic blood pressure response to handgrip exercise was in the borderline range in four of the eight patients with symptomatic autonomic dysfunction (two in each group) as well as in one asymptomatic group 1 patient, in the abnormal range in two symptomatic group 1 patients and normal in all others. Baseline contractility and the response to dobutamine were not influenced by the presence of autonomic neuropathy in either group. Furthermore, the high ejection fraction at rest in group 2 patients did not correlate with the presence of autonomic neuropathy because it did not differ in the five patients without and the four patients with evidence of autonomic dysfunction.

Total glycosylated hemoglobin levels. The glycosylated hemoglobin levels for the group 1 and group 2 patients were similar (group 1, 10.9 ± 0.7%; group 2, 10.7 ± 0.8%) and

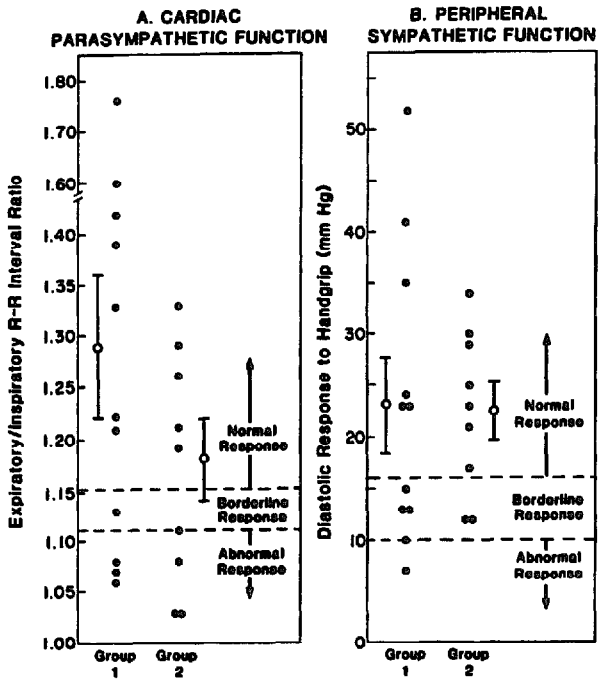


Figure 4. Autonomic nerve tests in patients with diabetes consisted of expiratory/inspiratory RR interval ratio as a measure of cardiac parasympathetic function and diastolic blood pressure response to handgrip exercise as a measure of peripheral sympathetic function. In both diabetic groups, a wide range of cardiovascular autonomic responses was present and the majority of patients had a normal response.

significantly higher than normal (5.2 ± 0.5%; $p < 0.001$). These levels, which reflect poor glycemic control, are representative of levels routinely encountered in the general diabetic population.

Funduscopic examination. No differences existed in the presence of retinal microangiopathy between the diabetic groups as detected by funduscopic examination. In group 1, 6 (55%) of 11 patients had evidence of retinal microangiopathy whereas in group 2, 5 (56%) of 9 patients had such findings. Therefore, the difference in exercise ejection fraction response between the diabetic groups could not be accounted for by differences in small vessel disease.

Discussion

Prior studies of cardiovascular function in young adult patients with long-standing diabetes have considered the cardiovascular system as a black box with physiologic or pharmacologic perturbations as inputs and indexes of overall cardiac performance (such as ejection fraction and cardiac output) as the most commonly measured outputs. However, the ability to differentiate abnormalities in overall cardiac performance due to alterations in ventricular contractility from those due to abnormal loading conditions is critical, because it is the magnitude of ventricular contractile dysfunction in a given patient that determines much of the subsequent risk for cardiac symptoms. Accordingly, the ability to define the physiologic derangement in a given patient is important in order to understand and pursue appropriate therapeutic options. The current study, which used load-independent indexes to assess left ventricular inotropic state, demonstrated that baseline ventricular contractility and contractile reserve were normal in a cohort of patients <40 years of age with long-standing diabetes mellitus in the absence of ischemic heart disease regardless of their ejection fraction response to exercise. Neither the presence of autonomic dysfunction nor microvascular abnormalities (as assessed by funduscopic examination for retinal microangiopathy) correlated with abnormal radionuclide studies. To interpret the physiologic importance of these results, it is useful to reevaluate the prior evidence for left ventricular contractile abnormalities in patients with diabetes.

Assessment of baseline contractility. Previous clinical studies of baseline left ventricular performance in young patients with diabetes have used systolic time intervals (1–5), echocardiography (1,2,6,7) and radionuclide angiographic methods (8,9). From all of these studies, it appears that baseline left ventricular contractility can be either normal or depressed in pediatric as well as adult patients with diabetes (10). However, proper interpretation of the data from these studies is difficult because all of the investigators used traditional indexes of overall ventricular performance that are highly load dependent. Although these measurements are adequate to assess net ventricular function, they are unable to separate changes in contractility from alterations in preload and afterload. This is especially important in patients with diabetes, because they have been reported (36–39) to have abnormalities in ventricular preload or diastolic filling, or both.

Assessment of left ventricular contractile reserve. A standard method for assessing contractile reserve in patients considered at risk for cardiomyopathy is to quantitate the ejection fraction response to dynamic exercise. This technique has been used in young adult patients with diabetes in an attempt to unmask cardiovascular abnormalities that are not evident under rest conditions. Mildenberger et al. (8) performed radionuclide ventriculography at rest and during exercise in 20 patients with diabetes aged 21 to 44 years. None of these patients had evidence of coronary artery disease, systemic hypertension or any other cardiac abnormalities. Results were compared with findings from 18 age-matched normal subjects. There were no differences between the diabetic and control groups with respect to heart rate or left ventricular ejection fraction at rest. With exercise, ejection fraction decreased in 7 of the 20 patients with diabetes and 1 of the 18 control subjects. Ejection fraction response during exercise in the patients with diabetes did not correlate with age, gender, duration of diabetes,

Table 3. Combined Radionuclide Angiographic Data

	Normal Subjects	Patients With Diabetes	
		(ΔLVEF > 0)	(ΔLVEF ≤ 0)
Number of patients	48	45	25
Left ventricular ejection fraction (LVEF)			
Rest conditions (%)	65 ± 6	63 ± 6	71 ± 5*‡
Peak exercise (%)	75 ± 8§	72 ± 8§	65 ± 6†§
Change (% units)	10 ± 7	9 ± 6	−6 ± 6*‡

*$p < 0.001$, normal subjects versus patients with diabetes (ΔLVEF ≤ 0); †$p < 0.017$, normal subjects versus patients with diabetes (ΔLVEF ≤ 0); ‡$p < 0.001$, patients with diabetes and ΔLVEF > 0 versus patients with diabetes and ΔLVEF ≤ 0; §$p < 0.001$, exercise versus rest LVEF. Based on data from References 8 and 9 and current study.

retinopathy, peak rate-pressure product, work load attained or ECG findings. The authors (8) concluded that one third of patients with diabetes had subclinical left ventricular dysfunction without correlation to risk factors for atherosclerosis or other diabetic complications. In another study, Vered et al. (9) used radionuclide techniques at rest and during bicycle exercise to study 30 men with diabetes (ranging in age from 21 to 35 years) and 20 age-matched control subjects. There was no difference in rest left ventricular ejection fraction between the patients and control subjects. However, 43% of the patients with diabetes decreased or had an unchanged ejection fraction with exercise, whereas all of the normal subjects had an increased ejection fraction. In the patients with diabetes in whom ventricular dysfunction was noted, it was always of the global, diffuse form without perfusion defects by thallium imaging. The authors (9) concluded that diabetes causes exercise-induced global left ventricular dysfunction in young patients without known heart disease. Although these reports suggest that contractile reserve is decreased in many asymptomatic patients with diabetes, careful analysis of the techniques used to acquire this information raises other possible interpretations of the data. As noted earlier, the acute physiologic adjustments to dynamic exercise that result in an increase in ejection fraction include peripheral vasodilation in exercising muscle, neurally mediated increases in sympathetic tone to the heart and periphery, release of catecholamines from the adrenal gland and changes in systemic venous tone influencing venous return and, subsequently, ventricular preload (11,12). Derangement of any one of these mechanisms can result in an abnormal ejection fraction response to exercise when left ventricular contractile reserve is normal.

The autonomic nervous system modulates the heart rate and blood pressure responses to dynamic exercise (11). Many investigators (40,41) have shown a high incidence of cardiac autonomic abnormalities involving both the parasympathetic and sympathetic nervous systems in patients with diabetes, especially those with peripheral neuropathy. The expiratory/inspiratory ratio is widely regarded as a very sensitive and reproducible measure of cardiac autonomic involvement (23) and is usually abnormal before there are clinical findings of cardiac or extracardiac autonomic dysfunction in patients with diabetes. Although clinical and laboratory evidence of autonomic neuropathy was present in a number of our patients, autonomic dysfunction in itself did not explain the abnormal ejection fraction response to exercise. Furthermore, baseline contractility and the response to dobutamine were not influenced by the presence of autonomic neuropathy in either diabetic group.

Unifying hypothesis: a physiologic explanation. Because baseline left ventricular contractility and reserve were normal in our young adult patients with diabetes, the explanation for the abnormal ejection fraction response to upright dynamic exercise must lie with factors extrinsic to the contractile mechanism of the heart. One possibility would be an abnormality in cardiopulmonary coupling during dynamic exercise. However, this seems unlikely because ventilatory anaerobic threshold, phase-one oxygen uptake at the lungs and the time constant for oxygen consumption have been reported (42) to be normal in young adult patients with diabetes regardless of the presence of peripheral or cardiac autonomic neuropathy. An observation that may be important is the significantly higher upright rest ejection fraction present in those patients with diabetes who subsequently had a decreased ejection fraction with exercise. On retrospective examination, a similar finding was present but not commented on in both of the prior studies (8,9) of left ventricular ejection fraction response to upright dynamic exercise performed in nonischemic normotensive young adult patients with diabetes. Table 3 summarizes the combined radionuclide angiographic data from the 70 patients with diabetes and 48 normal subjects studied with very similar experimental protocols by Mildenberger et al. (8), Vered et al. (9) and ourselves. Twenty-five diabetic patients (36% of the combined cohort) did not augment ejection fraction at peak exercise. Rest ejection fraction was significantly higher for these patients ($p < 0.001$) than for the normal subjects or patients with diabetes who had an increase in ejection fraction.

These findings are consistent with the fact that one of the most important determinants of ejection fraction response to dynamic exercise is ejection fraction at rest. Indeed, when

Table 4. Effects of Position on Heart Rate and Overall Left Ventricular Performance in Diabetic Patients

	Group 1 (n = 11)	Group 2 (n = 9)
Heart rate (beats/min)		
Supine	79 ± 10	81 ± 9
Upright	81 ± 14	93 ± 11*†
Overall left ventricular performance		
Supine (%ΔD)	34.9 ± 3.4	34.7 ± 2.6
Upright (EF)	62 ± 4	73 ± 4‡

*$p < 0.01$ versus supine; †$p < 0.05$, group 1 versus group 2; ‡$p < 0.001$, group 1 versus group 2; %ΔD = left ventricular percent fractional shortening; EF = left ventricular ejection fraction.

rest ejection fraction is ≥70% in normal subjects, failure to increase ejection fraction with exercise is a common occurrence (43–46). As noted earlier, eight of nine group 2 patients with diabetes had rest ejection fraction values >70%. Why then was rest ejection fraction increased in our group 2 patients with diabetes? The answer may be explained by intergroup differences in the hemodynamic response to assuming the upright position required for the radionuclide studies. When the patients were studied in the supine position, no differences existed between the diabetic groups for heart rate, systemic blood pressures or overall ventricular performance. However, when studied in the upright position, heart rate and overall ventricular performance were significantly higher in the group 2 patients with diabetes (Table 4). Importantly, these differences in hemodynamic response cannot be explained by intergroup differences in tests of cardiac autonomic function (Fig. 4). Abnormalities in ventricular diastolic chamber compliance can result in a decreased ejection fraction response to exercise but cannot account for the elevated ejection fraction under upright rest conditions.

One possible physiologic explanation for all of our findings would be the presence of abnormalities in systemic venous tone in the group 2 patients with diabetes. If, on assuming the upright position, the systemic venous bed failed to appropriately maintain blood return to the heart, a decrease in left ventricular preload would occur. This, in turn, could lead to an increase in cardiac sympathetic tone resulting in the observed increase in heart rate and rest left ventricular ejection fraction. With dynamic exercise, this abnormality in systemic venous return would be overcome by the pumping action of skeletal muscles in the lower limbs. This improvement in venous return, when coupled with normal left ventricular contractile reserve, appropriate peripheral arteriolar dilation and a normally functioning adrenal medulla, would result in normal ejection fraction values at peak exercise. Indeed, despite the augmented rest ejection fraction for the group 2 patients with diabetes, no intergroup differences existed in our study patients for peak exercise ejection fraction.

Conclusions. When left ventricular systolic function was studied with indexes that control heart rate and loading conditions, no evidence was found to support the presence of a cardiomyopathy in young adult patients with long-standing diabetes without hypertension or ischemic heart disease despite the presence of autonomic neuropathy. In these patients, an abnormal ejection fraction response to dynamic exercise was an unreliable measure of contractile reserve, and thus, it should not be used as the sole indication for further diagnostic investigation or supportive therapy for a preclinical cardiomyopathy. Although heart disease is common in the >10 million patients with diabetes in this country, and the results of the current study suggest that intrinsic abnormalities in ventricular contractility cannot be implicated in the associated morbidity and mortality.

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