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Clin. Cardiol. 18, 276–282 (1995)

Myocardial Dysfunction and Abnormal Left Ventricular Exercise Response in Autonomic Diabetic Patients

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Summary: In diabetic patients, the pathophysiologic mechanisms of exercise-induced left ventricular (LV) dysfunction remain controversial. In this study, the role of myocardial contractility recruitment in determining an abnormal LV response to isometric or dynamic exercise has been investigated in 14 diabetic patients with autonomic dysfunction. Ischemic heat disease was excluded by the absence of LV wall motion abnormalities induced by isotonic and isometric exercise and by coronary angiography. Left ventricular and myocardial function were studied at rest, and during isometric and isotonic exercise, by two-dimensional echocardiography; moreover, recruitment of an inotropic reserve was assessed by postextrasystolic potentiation at rest and at peak handgrip. An abnormal response of LV ejection fraction to isometric (9/14) or to dynamic (8/14) exercise was frequent in study patients. In these patients, baseline myocardial contractility was normal, and the significant increase in ejection fraction by postextrasystolic potentiation indicated a normal contractile reserve (65 ± 7% vs. 74 ± 6%, p = 0.001). Nevertheless, the downward displacement of LV ejection fraction-systolic wall stress relationships during exercise suggests an inadequate increase in myocardial contractility. However, the abnormal ejection fraction at peak handgrip was completely reversed by postextrasystolic potentiation (67 ± 6% vs. 58.1 ± 10%, p = 0.008), a potent inotropic stimulation independent of the integrity of adrenergic cardiac receptors. A defective inotropic recruitment, despite the presence of a normal LV contractile reserve, plays an important role in de-

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Received: August 3, 1994
Accepted with revision: October 21, 1994

exercise LV dysfunction in diabetic patients with autonomic neuropathy.

Key words: myocardial function, contractility, diabetes, postextrasystolic potentiation, left ventricular function, exercise

Introduction

Heart disease is the major cause of mortality among diabetic patients[1,2] and the risk of cardiac failure is three- to five-fold higher than in nondiabetics. The mechanisms of myocardial dysfunction remain controversial and are, presumably, multifactorial. However, cardiac problems in diabetic patients cannot always be attributed to factors such as atherosclerosis, a combination of microangiopathy and macroangiopathy, and autonomic neuropathy, suggesting that a specific cardiomyopathy may be a causal factor in producing the increase in cardiac mortality and morbidity.[1,2] To study diabetic heart muscle disease, it is necessary to assess patients in a specific pathophysiologic context, to exclude the presence of other pathologic conditions possibly affecting myocardial performance (coronary or hypertensive heart disease), and to analyze left ventricular (LV) function distinguishing abnormalities in myocardial contractility from changes in load.[3,5]

In this study, we assessed LV mechanical performance by a noninvasive approach to pump function, wall motion, and myocardial contractility. This noninvasive approach was applied in diabetic patients with autonomic dysfunction without clinical evidence of hypertensive, ischemic, or valvular heart disease in order to characterize resting and exercise LV performance and its relation to myocardial function; the contractile reserve and its recruitment during exercise have been investigated by postextrasystolic potentiation.

Patients and Methods

Study Patients

The study population comprised 14 consecutive nonhypertensive patients with insulin-dependent diabetes mellitus and autonomic dysfunction (10 men and 4 women, age range 32–54 years), meeting the following criteria: (1) blood pressure < 150 mmHg systolic and < 90 mmHg diastolic, (2) serum creatinine < 1.2 mg/dl, (3) absence of electrocardiographic (ECG) signs and clinical history of myocardial infarction, (4) no angina pectoris, (5) absence of ischemic ST changes induced by exercise, (6) no LV wall motion abnormalities induced by isotonic or isometric exercise, (7) no evidence of valvular heart disease, (8) no evidence of significant obstruction in coronary vessels by coronary angiography. The duration of diabetes from the date of diagnosis was more than 10 years in all study patients. Insulin was the only drug received by the patients. All patients had a funduscopic examination specifically for evidence of retinal microangiopathy. All study patients gave their informed consent to the protocol.

Ten normal subjects comparable as to age and gender constituted the controls.

Tests of Cardiovascular Autonomic Nerve Function

Autonomic dysfunction was defined as an abnormal response to two or more of the five following autonomic tests:[6] heart rate response to Valsalva maneuver (a ratio of the longest RR interval after the maneuver to the shortest RR interval during the maneuver ≤ 1.1 is abnormal); heart rate response to deep inspiration (a variation of ≤ 10 beats/min^{-1} between inspiration and exhalation is abnormal); heart rate response to standing (a ratio of ≤ 1 between the shortest RR interval at 15 beats after standing and the longest RR interval at 30 beats after standing is abnormal); blood pressure response to changes in posture (autonomic dysfunction is indicated by a fall of ≥ 30 mmHg at 1 min after standing); blood pressure response to sustained handgrip (a failure of the diastolic blood pressure to rise ≥ 10 mmHg is abnormal).

Echocardiographic Analysis

Left ventricular function was assessed by two-dimensional (2-D) echocardiography at rest and during several interventions: sustained handgrip, upright bicycle exercise, and postextrasystolic potentiation. Echocardiographic examinations were performed with a Hewlett-Packard 77030A phase array ultrasonoscope and a 2.5 or 3.5 MHz transducer. Echocardiographic studies were coded and read by two independent observers blinded to the patient's identity and experimental condition. Echocardiographic analysis was performed by using digitized cineloops methods (Prevue III System, Nova Microsonics, Inc.).

Wall motion and myocardial thickening were detected from echocardiographic images of the left ventricle obtained in apical four- and two-chamber views and in parasternal long-axis and short-axis views. Left ventricular wall motion was analyzed by repeated viewing. Segments were judged normal, hypokinetic (severe reduction in systolic inward and thickening), akinetic (no systolic endocardial excursion and thickening), or dyskinetic (paridoxical endocardial excursion and thinning). Agreement of interobserver analysis for segmental asynergy was seen in 98% of the segments visualized. Discrepancies were resolved by consensus.

Left ventricular volumes were calculated by an ellipsoid biplane area-length method.[7] Ejection fraction was derived as EDV-ESV/EDV, where EDV and ESV were the end-diastolic and the end-systolic volume. Left ventricular endocardial echocardiograms in apical four- and two-chamber views, in a minimum of two to four cardiac cycles, were digitized at end-diastole (R wave peak) and at end-systole (time of smallest cavity area) by the two independent observers. A discrepancy greater than 10 ml for LV volume required the analysis of echocardiographic tracing by a third observer. Agreement was achieved by consensus. However, interobserver and intraobserver variability for LV area ($r = 0.94$, and $r = 0.98$, respectively) and for LV length ($r = 0.95$, and $r = 0.96$, respectively) was acceptable.

Peak arterial pressure/LV end-systolic volume ratio has been calculated as a noninvasive approximation of LV contractility[8] using simultaneous values of pressure and volume at baseline and at peak handgrip and dynamic exercise.

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.[9] Linear interpolation to the level of the incisura was then performed to estimate end-systolic pressure. Left ventricular end-systolic circumferential wall stress (kdyn/cm^2) was calculated as:[10] $S = (1.332PD/2h)(1\text{-}h/D\text{-}D^2/2L^2)$, where P is the end-systolic pressure (simultaneous with LV echocardiographic measurements), D is the LV end-systolic short-axis diameter (in parasternal short-axis view), L is the LV long axis (in apical four-chamber view), h is the LV wall thickness, and 1.332 is the factor to convert from mmHg to kdyn/cm^2. Wall stress was calculated at rest and during both isometric and isotonic exercise.

Isotonic Exercise

Patients underwent a maximal symptom-limited exercise test on bicycle, with 25 W increments every 2 min. Heart rate and QRS morphology were monitored continuously, and a 12-lead ECG was recorded before exercise, during hyperventilation, at the end of each stage of exercise and of each min during recovery. Systolic and diastolic blood pressures were measured by cuff method before exercise and at the end of each stage of exercise and of each min during recovery. The result of the test was considered positive for ischemia in the presence of ≥ 1 mm horizontal or downsloping ST-segment depression beyond an isoelectric baseline during exercise, lasting at least 1 min into recovery or occurring only in recovery. Stress induced hypotension, pulmonary congestion, and gallop rhythm were sought at the termination of exercise. Two-dimensional echocardiographic visualization of the left ventricle was performed before exercise and at each stage of exercise.

Isometric Exercise

Handgrip test was performed with the patient supine. Arterial pressure was measured every 30 s by oscillometric method (Nippon Colin Co. Ltd) and LV function was continuously monitored by 2-D echocardiography. Maximal voluntary contraction was determined by using a handgrip dynamometer Three minutes isometric exercise was performed at 40% maximal voluntary contraction. Patients were instructed to avoid performing the Valsalva maneuver during handgrip. Left ventricular function was assessed before and every 30 s during exercise. Heart rate was monitored continuously.

Postextrasystolic Potentiation

The technique used in our laboratory has been extensively described elsewhere.[11] By transesophageal cardiac stimulation, a single atrial extrastimulus was delivered every seventh sensed, spontaneous sinus beat and the induced extrasystole was progressively decreased by 10 ms obtaining a coupling interval varying from 500 to 300 ms (between the spontaneous and induced QRS complexes). The postextrasystole was then allowed to occur spontaneously according to the patient's intrinsic rhythm. During the procedure, LV volumes were monitored by 2-D echocardiography. We considered for analysis the beat with the maximum LV ejection fraction without significant changes in LV end-diastolic volume (increase < 10% from control value). Postextrasystolic potentiation was performed at rest and at peak handgrip in the diabetic patients.

Coronary Angiography

Coronary cineangiography was performed in all study patients by Judkins' technique: all examinations were evaluated by a blinded investigator.

Statistical Analysis

Data are expressed as mean values ± standard deviation. Each patient served as his own control. A paired *t*-test was used to assess changes in continuous variables. Intergroup comparisons were performed with an unpaired *t*-test that was corrected by using the Bonferroni method for multiple comparisons. Correlation and regression were determined with a linear least-squares method. All differences with a statistical probability of < 0.05 by a two-tailed approach were considered significant.

Results

Baseline Left Ventricular Function

Baseline characteristics of normal subjects and study patients are listed in Table I. Measurements of LV volume (64 ± 9 ml/m^2, range 54–74) and ejection fraction (66 ± 6%, range 58–70) in the control group were used to determine the mean and the 95% confidence limits of normal values. In diabetic patients, the baseline mean values of LV end-diastolic volume and ejection fraction did not differ in comparison with control. Six patients had an enlarged left ventricle as indicated by a ventricular end-diastolic volume index more than the upper limit of normal. All patients but two had normal ejection fraction; the remaining two

TABLE I Baseline characteristics

	Normals	Diabetics	p Value
HR (beats/min)	62 ± 14	89 ± 12	< 0.001
SBP (mmHg)	122 ± 7	134 ± 16	NS
DBP (mmHg)	76 ± 7	75 ± 7	NS
LVEDVI (ml/m^2)	64.8 ± 9.1	66 ± 16	NS
LVEF (%)	66 ± 6.5	65 ± 6.8	NS
PAP/ESV (mmHg/ml/m^2)	6 ± 1.8	5.7 ± 1.7	NS

Abbreviations: HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, LVEDVI = left ventricular end-diastolic volume index, LVEF = left ventricular ejection fraction, PAP/ESV = peak arterial pressure/end-systolic volume.

patients had an ejection fraction greater than the upper limit of normal. Peak systolic arterial pressure to LV end-systolic volume ratio of diabetic patients did not differ from normal values (5.7 ± 1.7 vs. 6.0 ± 1.8, p = NS).

Response to Handgrip

Isometric exercise did not provoke LV wall motion abnormalities or ST changes suggestive for myocardial ischemia in both diabetic patients and control subjects. Systolic blood pressure increased at peak exercise in both diabetics (134 ± 16 vs. 154 ± 26 mmHg, p = 0.002) and normals (122 ± 7 vs. 148 ± 29 mmHg, p = 0.002). Heart rate increased in normals (62 ± 14 vs. 86 ± 10 beats/min, p = 0.01), but did not change significantly in diabetics (89 ± 12 vs.92 ± 15 beats/min, p = NS). Ejection fraction response to handgrip in the control group was characterized by an increase of ≥ 0.05 unit in all but two subjects who showed no change during isometric exercise (mean value from 66 ± 6% vs. 76.8 ± 8%, p = 0.005). Of the diabetic patients, 64.2% (9/14) showed a decline in ejection fraction of ≥ 0.05 unit. Of the remaining patients, three had a significant increase while two showed no change in ejection fraction. In diabetics, LV ejection fraction mean value at peak exercise did not differ from baseline mean value (63.3 ± 7% vs.58.1 ± 10%, p = NS) (Fig. 1A) but increased significantly in normals (66 ± 6.5% vs. 76.8 ± 8%, p = 0.006). Patients with diabetes and an abnormal response to handgrip have similar values in resting ejection fraction in comparison with patients with a normal response and with normal subjects (64.8 ± 6%, 60.4 ± 7%, and 66 ± 6%, respectively, p = NS). In diabetic patients, peak arterial pressure to end-systolic volume ratio at peak handgrip did not change significantly from baseline values (5.72 ± 1.71 vs. 6.34 ± 2.82, p = NS), while it increased in normal subjects (6.0 ± 1.8 vs. 9.2 ± 1.4, p < 0.001) (Fig. 2A).

Response to Isotonic Exercise

Left ventricular wall motion abnormalities or ST changes suggestive for myocardial ischemia did not appear during exercise in any patients. In diabetic patients, systolic blood pressure increased (129 ± 23 vs. 174 ± 38 mmHg, p = 0.0001), while heart rate did not change significantly (99 ± 16 vs. 102 ± 19 beats/min, p = NS); mean peak workload did not differ from the control group (119 ± 28 vs. 124 ± 24 W, p = NS). Left ventricular end-diastolic volume index increased significantly in diabetic patients (53 ± 9 vs. 68 ± 12 ml/m^2, p = 0.0009). In normals, peak exercise mean ejection fraction increased from 69 ± 9% at rest to 79 ± 7% (p = 0.002), and all subjects had a significant improvement in LV ejection fraction at peak exercise. In diabetics, peak exercise ejection fraction did not vary significantly from baseline (66.6 ± 6.5% vs. 66.8 ± 10%, p = NS), (Fig. 1B) and was significantly lower in comparison with normal subjects (66.8 + 10% vs. 79 it 7%, p = 0.001) (Table II). In fact, eight (57.1%) diabetic patients had a decrease or no significant change in LV ejection fraction during exercise. Moreover, the peak arterial pressure to end-systolic volume ratio at

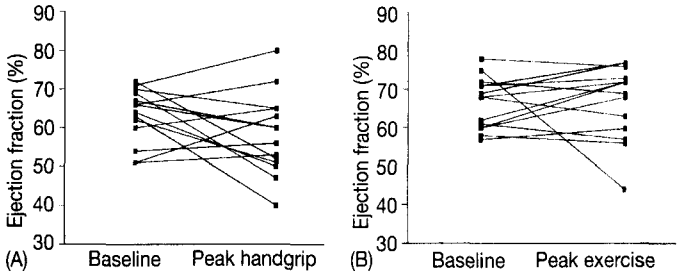

FIG. 1 Changes in left ventricular ejection fraction (EF) at peak handgrip (A) and at peak isotonic exercise (B) in diabetic patients.

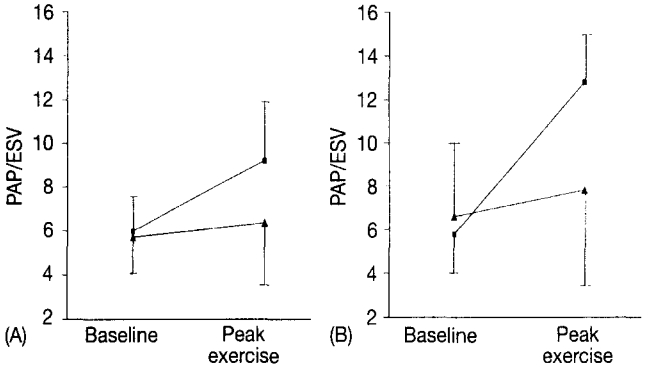

FIG. 2 Changes in peak arterial pressure (PAP)/end-systolic volume (ESV) ratio at peak handgrip (A) and at peak upright bicycle exercise (B) in diabetic patients. ■ = Normals, ▲ = diabetics.

peak exercise increased very significantly in normal subjects (5.8 ± 1.9 vs. 12.8 ± 2, p < 0.0001) while it did not change in study patients (6.6 ± 3.6 vs. 7.8 ± 4.4, p = NS) (Fig. 2B). Diabetic patients had similar response to exercise independent of the presence of a dilated or a normal-sized left ventricle: the mean values in LV ejection fraction at peak handgrip (56 ± 6% vs. 59.8 ± 8%, p = NS) and at peak bicycle exercise (68.5 ± 6% vs. 65.2 ± 8, p = NS) did not differ, and a similar percentage of patients in She two subgroups showed an abnormal response to isometric (62% vs. 66%, p = NS) and isotonic (57% vs. 57%, p = NS) exercise. Resting ejection fraction values did not differ in patients with abnormal response to dynamic exercise, in patients with a normal response, and in normal subjects (65 ± 5%, 67 ± 8%, and 66 ± 6%, respectively, p = NS).

Circumferential Wall Stress-Ejection Fraction Relation

When control points obtained at rest and during exercise from all 10 normal subjects were considered, the relation between LV circumferential wall stress and ejection fraction during exercise was linear. The correlation coefficient was 0.84 and 0.86 for handgrip and dynamic exercise, respectively. As shown in Figure 3A and B, there was impairment of ejection performance that was disproportionate to the degree of afterload in nine patients during handgrip and in eight during bicycle exercise.

TABLE II Peak exercise left ventricular function

	LVEDVI (ml/m²)	EF (%)	ESWS (kdyn/cm²)	PAP/ESV (mmHg/ml/m²)	HR (beats/min)	SBP (mmHg)
Isometric exercise						
Normals	76 ± 9	76.8 ± 8	220 ± 29	9.2 ± 1.4	96 ± 10	148 ± 29
Diabetics	79 ± 14	58.1 ± 6	238 ± 42	6.3 ± 2.8	92 ± 15	154 ± 26
p Value	NS	0.001	NS	0.001	NS	NS
Isotonic exercise						
Normals	72 ± 14	79 ± 7	255 ± 44	12.8 ± 2	154 ± 27	185 ± 32
Diabetics	68 ± 12	66.8 ± 10	269 ± 36	7.8 ± 4.4	102 ± 19	174 ± 38
p Value	NS	0.001	NS	0.001	0.001	NS

Abbreviations: LVEDVI = left ventricular end-diastolic volume index, EF = ejection fraction, ESWS = left ventricular end-systolic circumferential wall stress, HR = heart rate, SBP = systolic blood pressure.

Postextrasystolic Potentiation

Left ventricular ejection fraction increased significantly in the potentiated beat in all study patients (65 ± 7% vs. 74 ± 6%, p = 0.0001) independent of LV resting dimension, LV ejection fraction at rest, and response to exercise. To further clarify the etiology of depressed ejection performance in diabetic patients with abnormal response to isometric exercise (64.8 ± 6% vs. 53 ± 7%, p = 0.002), postextrasystolic potentiation was performed at peak handgrip: peak exercise postextrasystolic potentiation increased ejection fraction significantly in comparison with control peak value (67 ± 6% vs. 58.1 ± 10%, p = 0.008) (Fig. 4); potentiated peak handgrip ejection fraction did not differ from resting values (67 ± 6% vs. 63.3 ± 7%, p = NS) and was significantly lower than potentiated values at baseline (67 ± 6% vs.76 ± 6%, p < 0.0001). Moreover, the mean value of ejection fraction at peak isometric exercise was significantly lower than that in resting potentiated beat (58.1 ± 10% vs. 74 ± 6%, p = 0.001), and the mean value in LV ejection fraction at peak dynamic exercise was lower than resting potentiated beat (66.8 ± 9% vs.74 ± 6%, p = 0.027). In diabetic patients with normal response to at least one exercise, the peak exercise ejection fraction value did not differ from potentiated beat (73.7 ± 3% vs.74 ± 4%, p = NS).

Left Ventricular End-Diastolic Dimension

Baseline LV end-diastolic volume of diabetic patients did not differ from normal subjects in supine or in upright position. Left

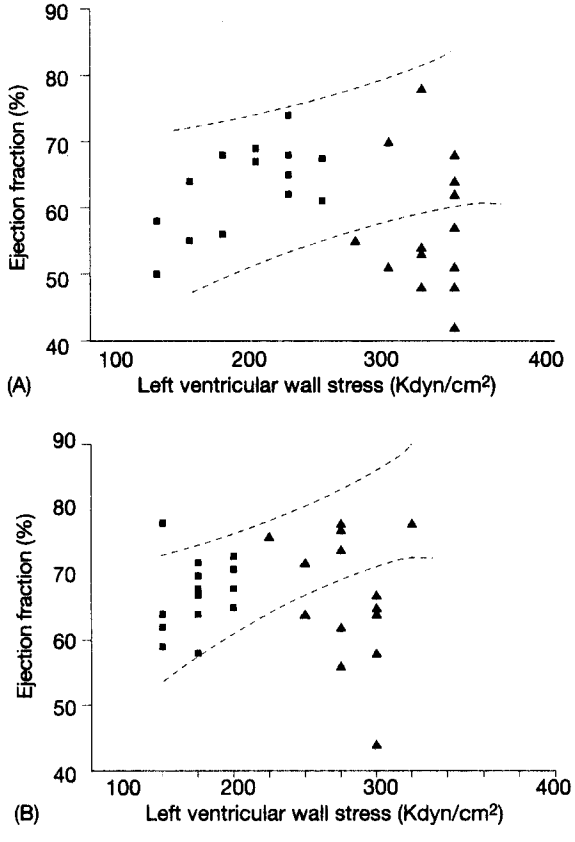

FIG 3 Relationship between ejection fraction and left ventricular circumferential end-systolic wall stress during isometric exercise (A) and isotonic exercise (B). Dashed lines represent the 95% confidence limits of relationship in normals. ■ = Baseline, ▲ = peak exercise.

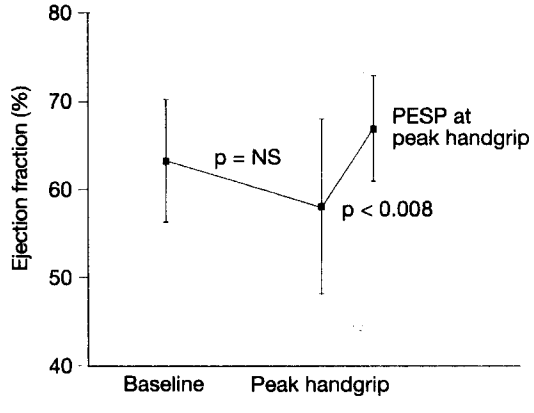

FIG. 4 Variation in ejection fraction from baseline to peak isometric exercise (p = NS) in diabetic patients; postextrasystolic potentiation (PESP) at peak handgrip elicits a significantly higher ejection fraction, revealing a normal contractile reserve.

ventricular end-diastolic volume diminished significantly at changing posture, and the magnitude of reduction was similar in diabetics and normals (22 ± 8% vs. 23 ± 9%, p = NS). Finally, changes in LV end-diastolic volume during exercise were similar in normals and diabetics, with a slight significant increase both at peak handgrip and peak bicycle exercise (Table II).

Funduscopic Examination and Coronary Angiography

Of the diabetic patients, 54% had evidence of retinal microangiopathy which was independent of LV ejection fraction response to exercise. This makes it unlikely that small vessel disease plays any role in influencing LV exercise performance.

Significant (> 50%) coronary stenosis could not be detected in any patient.

Discussion

Patients with insulin-dependent diabetes mellitus have an increased likelihood of developing congestive heart failure independently of coronary atherosclerosis and/or hypertension.[1, 2, 12, 13] Several prior studies have demonstrated an abnormal response of LV ejection fraction to exercise in a large subset of young adult patients,[12–16] although baseline myocardial contractility was normal.[5] Thus, in this study we assessed LV performance in adult patients with insulin-dependent diabetes, autonomic dysfunction, and a duration of the disease longer than 10 years.

Exercise Left Ventricular Function and Contractile Recruitment

In our study patients, contractile reserve, defined as the capacity to improve LV pump function by postextrasystolic potentiation, was normal regardless of ejection-fraction response to exercise. Postextrasystolic potentiation represents an inotropic stimulation that can recruit the maximal inotropic reservoir independent of load variation and in close relation to the integrity of contractile machinery.[17, 18] The variation of LV pump function and contractility induced by postextrasystolic potentiation has been employed in different clinical subsets, including coronary artery disease and congestive heart failure, with significant clinical and prognostic implications.[11, 19, 20]

An insufficient improvement in myocardial contractility during exercise has been demonstrated in our patients when analyzing the exercise-induced changes in peak systolic arterial pressure/LV end-systolic volume ratio and the LV circumferential wall stress-ejection fraction relationships. Left ventricular chamber elastance has been shown to be independent of preload and afterload.[21] A noninvasive approximation of end-systolic elastance can be obtained from the relation between the peak systolic arterial pressure and LV end-systolic volume detected by echocardiography.[8, 22] However, the need for simultaneous pressure and volume measurements over a wide range of loading variations makes this relation not easily feasible in the clinical setting.[23] Thus, the peak arterial systolic pressure to end-systolic volume index ratio has been proposed as a simplified estimate of the slope of linear pressure-volume relation. This is a controversial simplification of myocardial contractility assessment obtained from analysis of a single beat. This ratio generally is independent of preload but is clearly affected by LV afterload.[24] However, it is probably safe to say that, if afterload increases and the ratio does not rise, the contractile function is depressed.[25] In our study, the increase of LV systolic stress was similar in controls and diabetics in both isotonic and isometric exercises. Nevertheless, the peak arterial pressure/end-systolic volume ratio increased significantly in normals, but failed to change significantly in diabetic patients. Thus, the inadequate improvement of this ratio indicates an inappropriate recruitment of contractility during both isometric and isotonic exercises.

The afterload-ejection fraction relationship has been used to examine myocardial contractility in papillary muscle[26] and in clinical investigations.[27–29] The response of the left ventricle to a sustained increase in afterload during exercise in normals is described by a linear correlation. Several diabetic patients were downwardly displaced and fell below the confidence interval defined by the control group. The decrease of the afterload-ejection fraction relationship below the 95% confidence interval of normals at each comparable level of afterload shows an inadequate increase in myocardial contractility during exercise in diabetic patients despite a normal contractile reserve at peak handgrip. Thus, a defective recruitment of contractility seems to be a major cause of LV dysfunction during exercise.

Myocardial ischemia was not a cause of exercise LV dysfunction in our study patients: in fact, LV dysfunction induced by exercise was always of the global, diffuse form without regional asynergy, and coronary angiography discovered no significant coronary obstructions; moreover, neither angina nor ST changes occurred: this is in accordance with a previous study in which no perfusion defects by thallium imaging were associated with LV dysfunction in patients with diabetes.[13] Finally, the normal increase in LV end-diastolic volume index at peak handgrip and peak bicycle exercise indicates that venous return was not a limiting factor in abolishing the normal ejection fraction response during exercise. Higher values in resting ejection fraction have been previously described in diabetics with abnormal response to exercise.[5] This observation cannot be confirmed by our study; in fact, patients with diabetes and abnormal response to isotonic or isometric exercise have ejection fraction values comparable with those of normals and of patients with a normal exercise response. Thus, in diabetic patients with autonomic dysfunction and an abnormal LV response to exercise, myocardial impairment has to be interpreted as a defective exercise recruitment of an otherwise normal contractile reserve.

Possible Pathophysiologic Mechanisms for the Defective Contractile Recruitment

Tachycardia and adrenergic stimulation of the myocardium exert complementary influences during exercise,[30] but adrenergic stimulation has a far greater effect. In diabetics with autonomic dysfunction, heart rate did not increase further with ex-

ercise, and this has deprived the heart of a major inotropic stimulus. Moreover, the abnormal contractile response during exercise in diabetic patients may be related to the defective cardiac inotropic response to catecholamines demonstrated in animal studies.[31–33] Thus, functional impairment of cardiac sympathetic nerve fibers and the reduced amount of cardiac catecholamines may contribute to a blunted and inadequate contractile increase during exercise. Postextrasystolic potentiation can normalize ejection fraction at peak handgrip, because this inotropic stimulus requires only the integrity of the contractile machinery and is independent of the integrity of adrenergic receptors.

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