Cardiac Metabolism

Effects of Insulin-Glucose Infusion on Left Ventricular Function at Rest and During Dynamic Exercise in Healthy Subjects and Noninsulin Dependent Diabetic Patients

A Radionuclide Ventriculographic Study

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OBJECTIVES   The aim of this study was to evaluate: 1) the effects of insulin administration on left ventricular ejection fraction (LVEF) during exercise, and 2) the eventual impairment of the cardiovascular response to insulin in noninsulin dependent diabetes mellitus.

BACKGROUND   Insulin influences the cardiovascular system, but its effect on left ventricular function has yet to be established.

METHODS   The effects of normal saline (test A) and insulin-glucose (insulin = 1.7 mU·kg^{-1}·min^{-1}; glucose = 6 mg·kg^{-1}·min^{-1}) (test B) infusions on systolic and diastolic functions at rest and during dynamic exercise were examined by radionuclide ventriculography. Twenty-two noninsulin-dependent diabetic patients and 22 gender, age and body mass index matched healthy subjects were investigated.

RESULTS   Both groups had normal scintigraphic parameters at rest and during dynamic exercise. Rest- and stress-LVEF as well as rest- and stress-peak filling rate were significantly ($p < 0.001$) lower in diabetic than in healthy subjects, both in test A and B. Rest-LVEF was significantly higher during test B than it was in test A only in diabetic subjects ($p < 0.01$). Stress-LVEF was significantly higher ($p < 0.05$) during test B than it was in test A, in both groups. Insulin-glucose infusion did not modify rest- and stress-peak filling rate in either group. No difference in left ventricular end diastolic volume and in mean blood pressure was found between test A and B at rest and during exercise in either group. A significant linear correlation between LVEF and the index of insulin sensitivity was found in diabetic patients.

CONCLUSIONS   In both normal and diabetic humans, insulin induces a very important rise in LVEF after submaximal work. However, the rise is significantly lower in diabetic than in nondiabetic subjects. The increase in exercise-LVEF on insulin is likely due to an enhancement of ventricular contractility. Insulin resistance could justify the lower angioscintigraphic indexes in diabetic subjects. (J Am Coll Cardiol 2000;36:219–26) © 2000 by the American College of Cardiology

Various clinical and experimental studies have documented the influence of insulin on cardiac function. A direct inotropic effect of insulin on the myocardium has been demonstrated in cats (1) and lambs (2). In humans, a rise in left ventricular ejection fraction (LVEF) measured by radionuclide ventriculography has been observed in patients with acute myocardial infarction in response to a therapeutic regimen containing glucose, insulin and potassium given by intravenous infusion (3) although it is not known which constituent provokes the cardiac effect. A significant rise in LVEF was found by Fisher et al. (4) within 5 min of the

intravenous injection of insulin, before any measurable change in the blood glucose concentration had occurred. Avasthi et al. (5) reported significant increments in cardiac output after ingestion of mixed meals when circulating insulin levels physiologically rise. Baron et al. (6,7) recently established that physiological insulin concentrations lead under both steady-state and after an oral glucose load to significant increments in cardiac output and that this effect is impaired in insulin-resistant obese humans.

In this novel area of human research, two aspects have not been investigated until now: 1) the effects of insulin administration on LVEF during exercise, 2) the eventual impairment of the cardiovascular response to insulin in noninsulin dependent diabetes mellitus (NIDDM), a condition notoriously associated with insulin resistance.

This study aimed to explore these topics. Cardiac function was examined in healthy subjects and NIDDM patients

Abbreviations and Acronyms

ANOVA	=	analysis of variance
ISI	=	insulin sensitivity index
LVEDV	=	left ventricular end diastolic volume
LVEF	=	left ventricular ejection fraction
MBP	=	mean blood pressure
MCR-G	=	metabolic clearance rate of glucose
MCR-I	=	metabolic clearance rate of insulin
NIDDM	=	noninsulin-dependent diabetes mellitus
PFR	=	peak filling rate
SS-G	=	steady-state plasma glucose
SS-I	=	steady-state plasma insulin

using resting and exercise radionuclide ventriculography during both saline and double insulin-glucose infusion at prefixed rates.

METHODS

Subjects. The study was approved by the medical ethical committee of the Second University of Naples. Two groups of subjects (Table 1) were studied after informed consent was obtained: 22 NIDDM patients and 22 gender- age- and body mass index matched healthy volunteers, with normal 75g oral glucose tolerance and negative family history for NIDDM. Diabetic patients were in good metabolic control as judged by glycosilated hemoglobin (HbA$_{1c}$) levels with diet and oral hypoglycaemic agents (glybenclamide: 10–15 mg per day).

An accurate preliminary evaluation was carried out with the aim of minimizing the influence of factors other than diabetes on left ventricular function. No subject had signs, symptoms or history of heart disease, chronic alcoholism, anemia, electrolyte imbalances, hepatic or endocrine or renal diseases. Only subjects without risk factors for coronary artery disease other than diabetes were selected. All participants were nonsmokers and had blood pressure values <140/90 mm Hg, serum cholesterol <7.5 mmol/l, serum tryglicerides <1.8 mml/l and negative family history for coronary artery disease.

Subjects with ECG abnormalities at rest or with downsloping or horizontal ST segment depression during a treadmill maximal exercise electrocardiography performed according to the Bruce protocol (8) or with left ventricular segmental asynergy assessed by M-mode and two-dimensional echocardiography or with rest or stress myocardial perfusion imaging performed after infusion of 3 mCi of [201m]T1 suggestive of ischemic heart disease were not enrolled.

Microangiopathy was excluded by ophtalmological evaluation using direct fundoscopy within one month before the study and by measuring excretion of albumin on a timed 24-h collection of urine (all subjects studied had albumin excretion <20 mg/24 h).

No difference in autonomic neural function was detected between nondiabetic and diabetic subjects as assessed by the heart rate responses to deep breathing, to Valsalva maneuver and to standing and by the blood pressure response to standing (Table 2). These tests were in age-related normal ranges (9) for all subjects. Peripheral neuropathy was not evaluated, as it had no influence on left ventricular function (10).

Both healthy and diabetic groups were engaged in similar physical activity. None of the participants were taking any drugs other than glybenclamide.

Protocol. Each group underwent two multiple-gated radionuclide ventriculographies, one during infusion of normal saline (test A) and the other during a double insulin-glucose infusion at prefixed rates (insulin = 1.7 mU·kg^{-1}·min^{-1}; glucose = 6 mg·kg^{-1}·min^{-1}) (test B). The studies were randomly performed on two different occasions, five to seven days apart.

The consumption of glybenclamide, alcohol, tea and coffee was avoided for 12 h before and during each experiment.

Subjects were studied in the supine position in a quiet room at 20°C after an overnight 14-h fast.

The left arm was utilized for blood pressure measurements, using a mercury sphygmomanometer with systolic and diastolic blood pressures measured at Korotkoff's 1st and 5th sounds, respectively. Mean blood pressure (MBP) was calculated from the sum of diastolic blood pressure plus one-third of the arterial pulse pressure.

For the blood samples, a venous cannula was inserted retrograde in a right hand vein and flushed with saline at a rate of 0.5 ml·min^{-1}, the hand being maintained in a hand warmer at 65°C. For the infusions, a second cannula was inserted in a vein of the antecubital fossa of the same side.

In test B, insulin (Humulin R; Ely Lilly, Basingskoke, United Kingdom) was diluted in albumin, and normal saline was added to obtain a concentration of 1.7 mU per kg of patient body weight per milliliter, and a 50% dextrose solution was diluted with normal saline to obtain a concentration of 6 mg per kg of patient body weight per ml and added with K_2HPO_4 (~0.0038 me·Kg^{-1}·ml) to prevent hypokalemia and hypophosfatemia. Both solutions were infused at a rate of 1 ml per min.

Table 1. Clinical Characteristics of Subjects

	Age (yrs)	Gender (M/F)	BMI kg/m^2	Diabetes Duration (yrs)	HbA$_1$c (%)
Healthy subjects (n = 22)	39.8 ± 1.9	11/11	24.8 ± 0.9		4.4 ± 0.3
Diabetic subjects (n = 22)	40.6 ± 1.8	11/11	25.2 ± 0.9	3.9 ± 0.8	6.6 ± 0.2*

*p < 0.001.
BMI = body mass index.

Table 2. Autonomic Cardiovascular Tests

	Lying to Standing (30:15 ratio)	Deep Breathing (E:I ratio)	Valsalva Maneuver (max:min ratio)	Orthostatic Hypotension Diastolic (mm Hg)	Systolic (mm Hg)
Healthy subjects	1.24 ± 0.04	1.39 ± 0.05	1.53 ± 0.05	3.2 ± 2.1	7.9 ± 2.4
Diabetic subjects	1.22 ± 0.04	1.37 ± 0.04	1.52 ± 0.06	3.8 ± 1.7	8.2 ± 2.7

Autonomic neural function was assessed by four cardiac reflex tests: 1) heart rate response to standing (30:15 ratio), 2) heart rate response to the deep breathing at six breaths per min with calculation of the ratio of the longer RR-interval during expiration and the shortest RR-interval during inspiration, 3) the Valsalva maneuver and calculation of the ratio of the longest RR-interval after and the shortest RR-interval during the maneuver, 4) blood pressure response to standing.

Test A was performed by infusing normal saline at a rate of 2 ml per min to give the same fluid load as test B.

After obtaining a basal blood sample, insulin-glucose infusion (test B) was started and maintained for 120 min to achieve the steady-state condition. Infusion was maintained for 120 min also during test A.

Successively, scintigraphic acquisition at rest was made and, then, exercise started without stopping the saline or insulin-glucose infusion until completion of stress scintigraphic scan.

The stress consisted of supine dynamic exercise on a bicycle ergometer, beginning with 25 W at 60 rpm and increasing by 25 W steps over 2 min until reaching the 75 W load. This work was maintained for 4 min for the stress scintigraphic scan.

During exercise, the subjects were submitted to ECG-standard recordings every 2 min.

For radionuclide angiography, red blood cells were labelled "in vivo" with 25 mCi of ^{99m}Tc pertechnetate. The studies were carried out with a small field of view Gamma camera (Basicam SIEMENS, Erlangen, Germany) equipped with a low-energy, general purpose, parallel hole collimator. Energy discrimination was provided by a 20% window centered over the 140-keV photopeak of ^{99m}Tc. A five million count study was made in 45° left anterior oblique view with a 15° of caudal tilt, using the positioning of the camera, which maximized the separation of blood pool activity in the left and right ventricles. Data were acquired in frame-mode by computer-based electrocardiographic gating with a 1.5× digital zoom. The cardiac cycle was divided into 24 frames, and data for each frame were collected in a 64 × 64 matrix. The imaging rate was 50 frames/s (or 20 ms/frame) with a gate tolerance of ±5%. Left ventricular ejection fraction and peak filling rate (PFR) were calculated by a standard computed software (11,12). Left ventricular end diastolic volume (LVEDV) was calculated by the Massardo et al. (13) method. Angioscintigraphic parameters were evaluated at rest and at 75 W.

Blood samples for glucose, potassium and insulin determinations were taken at 0, 30, 60, 90, 100, 110 and 120 min and at the end of each work step. Plasma C-peptide levels were measured at 0 and 120 min only during test B to calculate the metabolic clearance rate of insulin. Plasma adrenaline and noradrenaline levels were assessed at rest, at

the steady-state condition and at the end of the last work step in both tests.

Heart rate (from electrocardiogram) and blood pressure values were taken at basal conditions, before starting exercise and every 2 min during dynamic exercise. Each blood pressure determination was an average of at least two measurements.

Calculations, analytic methods and statistics. Steady-state (90–120 min) plasma glucose (SS-G), steady-state plasma insulin (SS-I), metabolic clearance rate of glucose (MCR-G), insulin sensitivity index (ISI = MCR-G/SS-I·100) and metabolic clearance rate of insulin (MCR-I) were calculated for test B, as elsewhere reported (14).

Plasma glucose was measured by a glucose oxidase method (Beckman glucose analyzer II, Fullerton, California). Plasma insulin and C-peptide were assayed with radioimmunological technique using specific kits (INCSTAR Corporation, Stillwater, Minnesota). Plasma adrenaline and noradrenaline concentrations were determined by high performance liquid chromatography. Glycosylated hemoglobin A_{1c} was determined by column chromatography using a commercial kit (BIO-RAD, Hercules, California) (values less than 7.0% indicated good glycemic control in diabetic patients). Urine albumin was measured by radioimmunoassay technique; the lowest detection limit was 1.5 μg/ml.

Statistical analysis was made by one-way analysis of variance (ANOVA). When differences were significant, Student *t* tests for paired and unpaired data were performed. Effect of insulin on angioscintigraphic parameters in diabetic and healthy subjects was analyzed by multivariate two-way ANOVA with repeated measures. Simple regression was applied to evaluate correlations between ISI and scintigraphic parameters. The computer software package SPSS for Windows, version 7.5, was used.

The level of statistical significance chosen was p < 0.05. Data in the text and Tables 1 through 5 are expressed as mean ± SD.

RESULTS

During investigations, plasma glucose concentration was approximately kept at baseline, and none of the subjects experienced hypoglycemia (plasma glucose <2.8 mmol/l), chest pain or electrocardiographic abnormalities suggestive of myocardial ischemia. Regional wall motion during radio-
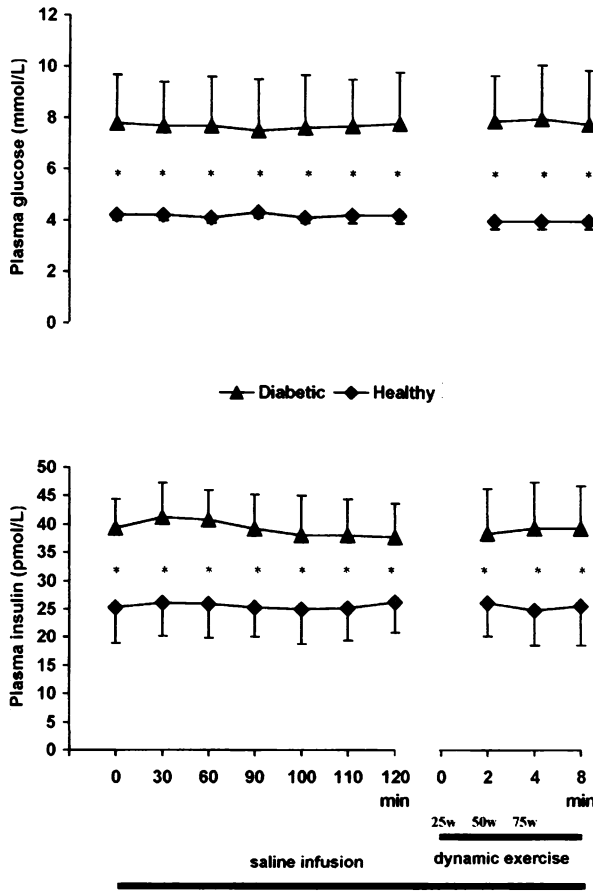
Figure 1. Insulin and glucose plasma levels during saline infusion (test A). *p < 0.001.

Figure 2. Insulin and glucose plasma levels during insulin-glucose infusion (test B). §p < 0.05; †p < 0.01; *p < 0.001.

nuclide angiography was normal in all subjects at rest or in response to exercise.

During exercise, patients and controls achieved 75% to 80% of the maximal ideal heart rate.

Metabolic/hormonal parameters. *Test A (Fig. 1).* Plasma glucose was significantly (p < 0.001) higher in diabetic than it was in healthy subjects during the whole test duration. Plasma insulin levels in diabetic patients were at all times significantly (p < 0.001) more elevated than it was in healthy subjects.

Test B (Fig. 2). Plasma glucose was significantly (p < 0.001) higher in diabetic than it was in healthy subjects during the entire test duration. Plasma insulin levels were significantly (p < 0.05 or less) higher in diabetic subjects at all times.

Basal and 120-min C-peptide levels were significantly (p < 0.05 or less) higher in diabetic subjects. Steady-state plasma glucose and SS-I were significantly (p < 0.01 or less) higher, whereas MCR-G, MCR-I and ISI were significantly (p < 0.01 or less) lower in diabetic subjects (Table 3).

Test A versus test B. Neither group experienced any significant difference between plasma glucose values during test A and B. Plasma insulin levels were significantly higher during insulin glucose-infusion (test B) than it was during saline infusion (test A) in both groups.
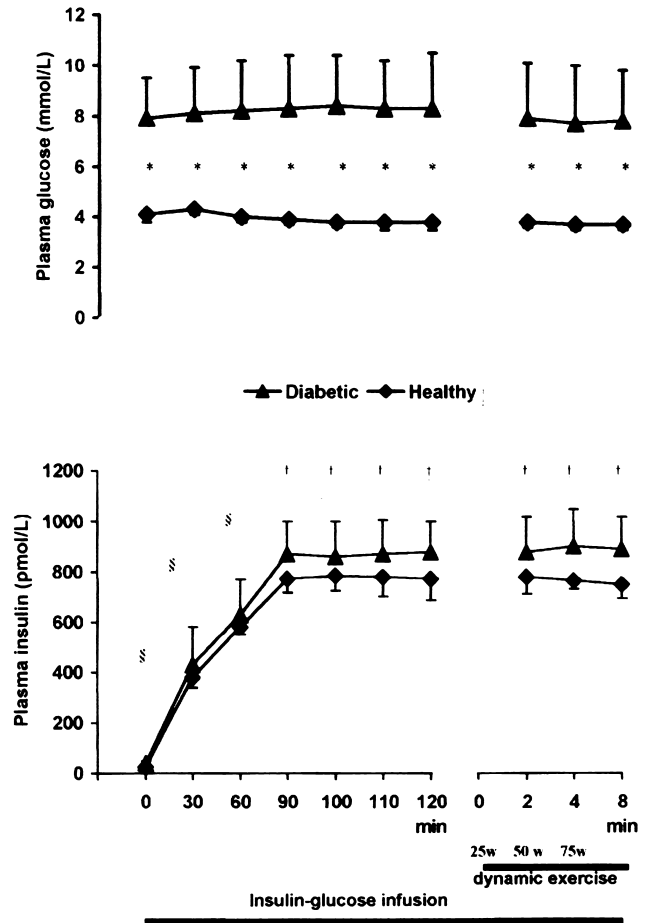
Similar rest and stress noradrenaline and adrenaline responses were observed between controls and diabetics in both tests (Table 4).

No significant difference in serum K^+ levels between groups was found during test A and B and between tests.

Angioscintigraphic parameters. Each healthy and diabetic subject showed a normal (>50%) LVEF at rest.

Diabetic versus healthy subjects (Table 5). During test A, resting and exercise-LVEF, resting and exercise-PFR and change in LVEF were significantly (p < 0.001) lower in

Table 3. Hormonal/Metabolic Parameters During Insulin-Glucose Infusion (Test B)

	Healthy Subjects	**Diabetic Subjects**
SS-G (mmol/L)	4.03 ± 0.53	7.93 ± 2.15‡
MCR-G (mg/kg/min)	9.1 ± 1.0	4.1 ± 1.2‡
SS-I (pmol/L)	789.1 ± 70.1	870.3 ± 122.4†
ISI	8.2 ± 1.0	3.2 ± 0.9‡
Basal CP (nmol/L)	0.85 ± 0.3	1.30 ± 0.51*
120 min CP (nmol/L)	0.74 ± 0.31	1.32 ± 0.43†
MCR-I (μU/kg/min)	17.1 ± 1.3	13.4 ± 1.4†

SS-G = steady-state plasma glucose; MCR-G = metabolic clearance rate of glucose; SS-I = steady-state plasma insulin; ISI = insulin sensitivity index; CP = plasma C-peptide; MCR-I = metabolic clearance rate of insulin.
*p < 0.05; †p < 0.01; ‡p < 0.001.

Table 4. Adrenaline and Noradrenaline Levels (nmol/l) During Saline (Test A) and Insulin-Glucose (Test B) Infusions

	Adrenaline	
	Healthy Subjects	**Diabetic Subjects**
Test A		
rest	0.443 ± 0.135	0.409 ± 0.089
stress	1.018 ± 0.084	0.870 ± 0.101
Test B		
rest	0.476 ± 0.123	0.401 ± 0.085
stress	1.051 ± 0.098	0.934 ± 0.102
	Noradrenaline	
	Healthy Subjects	**Diabetic Subjects**
Test A		
rest	0.391 ± 0.072	0.473 ± 0.161
stress	1.520 ± 0.131	1.571 ± 0.190
Test B		
rest	0.403 ± 0.082	0.493 ± 0.173
stress	1.590 ± 0.143	1.552 ± 0.181

diabetic subjects. No significant difference was found for rest-LVEDV and stress-LVEDV between the two groups.

During test B, resting and exercise-LVEF, resting and exercise-PFR and change in LVEF were significantly (p < 0.001) lower in diabetic subjects; the other parameters did not significantly differ between groups.

A significant positive correlation was found in diabetic patients between LVEF and ISI both at rest (r = 0.59; p < 0.004) and during exercise (r = 0.58; p < 0.005) (Fig. 3).

Test A versus test B (Table 5). Rest-LVEF was significantly higher during test B than test A in diabetic subjects (p < 0.01) but not in healthy subjects. Stress-LVEF was significantly higher (p < 0.05 or less) during test B than A,

Table 5. Angioscintigraphic Parameters During Saline (Test A) and Insulin-Glucose (Test B) Infusions

	Test A	
	Healthy Subjects	**Diabetic Subjects**
rest-LVEF (%)	67.0 ± 2.8	57.2 ± 2.0*
stress-LVEF (%)	72.3 ± 1.8	63.6 ± 2.6*
Change in LVEF	5.8 ± 1.6	6.4 ± 1.8*
rest-LVEDV (ml)	106.7 ± 6.0	112.1 ± 6.9
stress-LVEDV (ml)	94.3 ± 12.3	100.1 ± 13.5
rest-PFR (LVEDV/s)	2.8 ± 0.4	2.1 ± 0.4*
stress-PFR (LVEDV/s)	6.8 ± 1.9	4.7 ± 1.0*
	Test B	
	Healthy Subjects	**Diabetic Subjects**
rest-LVEF (%)	69.5 ± 1.7	64.6 ± 2.0*†
stress-LVEF (%)	81.9 ± 1.5‡	70.0 ± 2.7*§
Change in LVEF	12.0 ± 1.6‡	5.4 ± 1.3*†
rest-LVEDV (ml)	106.8 ± 6.9	115.3 ± 11.4
stress-LVEDV (ml)	98.3 ± 9.8	102.4 ± 14.6
rest-PFR (LVEDV/s)	2.8 ± 0.3	2.2 ± 0.4*
stress-PFR (LVEDV/s)	6.3 ± 2.0	4.8 ± 1.2*

LVEF = left ventricular ejection fraction; change in LVEF = variation of LVEF on exercise; LVEDV = left ventricular end diastolic volume; PFR = peak filling rate.
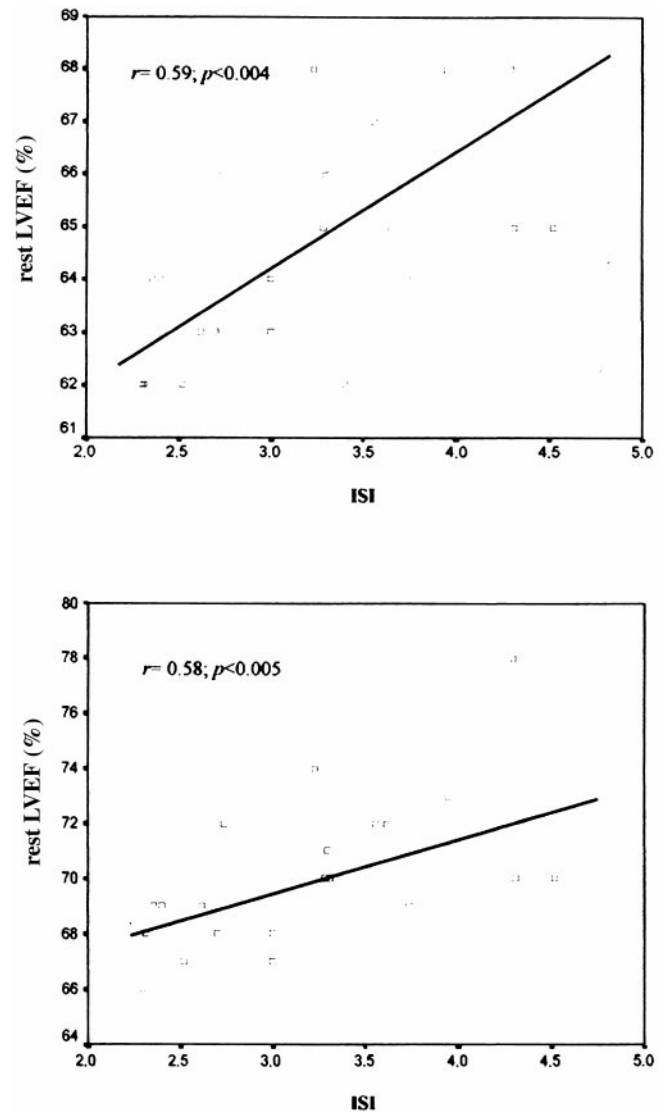*p < 0.001 (healthy vs. diabetic subjects); †p < 0.01; ‡p < 0.001 (test A vs. test B); §p < 0.05.

Figure 3. Relation between LVEF and ISI both at rest **(top)** and during exercise **(bottom)** in diabetic patients.

in both groups. Change in LVEF was significantly (p < 0.001) higher in healthy subjects and significantly (p < 0.01) lower in diabetic patients during test B. The differences in the other parameters were statistically insignificant for both groups.

Two-way repeated measures ANOVA (Table 6). The study of interaction between test A versus test B and diabetic versus healthy subjects showed that the effect of insulin in diabetic and healthy subjects was statistically different (p < 0.0001) in rest-LVEF, stress-LVEF and change in LVEF. **Heart rate and blood pressure.** No significant difference in heart rate or MBP was found between healthy and diabetic subjects in test A and B and between test A and B.

DISCUSSION

This study primarily aimed to explore the effect exerted by a double infusion of insulin and glucose at prefixed rates on

Table 6. Two-Way Repeated Measures ANOVA

	Sources of Variability	F
Rest-LVEF	diabetic vs. healthy subjects	204.912
	test A vs. test B	150.118
	interaction	64.369*
Stress-LVEF	diabetic vs. healthy subjects	354.245
	test A vs. test B	437.517
	interaction	18.711*
Change in LVEF	diabetic vs. healthy subjects	58.414
	test A vs. test B	80.685
	interaction	144.496*

*$p < 0.0001$.
ANOVA = analysis of variance.

cardiac function at rest and in response to supine dynamic exercise in healthy and NIDDM subjects.

The results seem to indicate that, in healthy subjects, supraphysiological plasma levels of insulin are able to substantially increase LVEF in response to submaximal dynamic exercise, whereas they do not influence this parameter at rest. An echocardiographic study (15) has also shown that moderate hyperinsulinemia, induced by intravenous insulin infusion with euglycemic clamp technique, has no effect on ejection phase indexes in healthy supine subjects. Conversely, there is no data in the literature concerning insulin's effect on left ventricular function during dynamic stress.

Cardiovascular effects of insulin. The mechanism underlying the cardiovascular effects of insulin and their evaluation are complex. In agreement with some authors (16) but not with others (17), we found no difference in left ventricular end diastolic volume or in blood pressure between saline and insulin-glucose infusion. Thus, an influence of preload or afterload on LVEF can be reasonably excluded, and the observed modifications of LVEF on insulin likely express the status of left ventricular contractility.

In agreement with the literature (18–20) diabetic patients showed an impaired diastolic function compared with healthy subjects, both at rest and during exercise, as evaluated by PFR. Moreover, insulin-glucose infusions do not modify these diastolic parameters in either group.

The first question to be addressed is whether the increase in ejection fraction during exercise observed for insulin is an expression of the hormone's direct action on the heart.

The similar heart rate changes from rest to exercise with or without insulin-glucose infusion do not suggest changes in sympathetic drive, as confirmed by plasma catecholamine levels.

A direct inotropic effect of insulin has been suggested by some authors. Experimental studies on cats and lambs have shown that intravenous insulin increases myocardial contractility, without being mediated by glucose or catecholamine (1,2). However, studies on dogs and rats have failed to demonstrate a positive inotropic effect in either intact hearts or isolated cardiac muscle (21–23).

Metabolic hypothesis. We hypothesize that enhanced left ventricular function observed after insulin may be due to the metabolic effects of the hormone. In resting fasting humans, heart muscle takes up significant amounts of free fatty acids, lactate, pyruvate, glycerol and beta-hydroxybutyrate, that is, it preferentially uses substrates that yield energy through mitochondrial metabolism, while glycolysis normally produces only ~30% of energy (24–28). Physiological hyperinsulinemia specifically enhances myocardial glucose, lactate and pyruvate uptake, converting cardiac fuel reliance from fat to carbohydrate (16). A similar shift of circulating substrate uptake and oxidation by the heart has been observed during atrial pacing (29). Conversely, during exercise lactate becomes the most important source of energy for the heart (26). These findings suggest that hyperinsulinemia during dynamic stress may increasingly favor myocardial carbohydrate oxidation and, consequently, improve cardiac performance in healthy subjects.

Role of diabetes on systolic function. The noninsulin-dependent diabetic patients we examined by radionuclide angioscintigraphy showed normal LVEF and normal rise in this parameter on supine dynamic exercise. Nevertheless, their LVEF at rest and under stress and both on saline or insulin was significantly lower than that of a healthy population matched for age, gender and body mass index.

Our diabetic patients were relatively young; disease duration was short, and they were in good metabolic control. Moreover, coronary artery disease, microangiopathy, autonomic neuropathy and any cardiovascular abnormalities detectable by noninvasive techniques were excluded early. Due to these strict exclusion criteria, it is reasonable that only diabetes could have conditioned this depressed, albeit normal, systolic function in the diabetic group. The use of glybenclamide could have played a role. However, a positive (rather than negative) inotropic effect on the heart has been reported only for tolbutamide (30). In this regard, no data are available for second and third generation sulphonylureas.

Unlike healthy subjects, the LVEF of diabetic patients after insulin significantly increased not only during exercise but even at rest. However, despite the higher steady-state that plasma insulin levels reached during insulin-glucose infusion (likely induced by their lower metabolic clearance rate of the hormone), the diabetic group showed a significant decline in the percent rise of the ejection fraction in response to work.

These differences cannot be justified by the behavior of afterload, preload or catecholamine levels.

If it is true that the increment of the exercise-LVEF on insulin in healthy subjects is mediated by the metabolic effects of the hormone, the lower angioscintigraphic indexes observed in NIDDM subjects could be justified by their insulin resistance, as suggested by the significant linear correlation between LVEF and the ISI found in these patients.

In diabetic patients at rest, insulin infusion partially compensates the gap with the healthy subjects, by improv-

ing the yield of metabolic glucose pathways and cardiac performance. In the same patients, the stress-induced increase of LVEF is, conversely, less important during insulin than during saline infusion, perhaps because of overburdened heart glucose metabolism.

Metabolism in the diabetic heart. This may be in agreement with the finding of metabolic defects within myocardial postreceptors in a streptozotocin-induced rat model of NIDDM, which lead to a significant basal and insulin-stimulated reduction in glucose oxidation and ATP synthesis from glucose (31) and a parallel decrease in the maximal stimulation of cardiac work by insulin (32). However, studies on humans utilizing positron emission tomography to determine regional glucose utilization rates have failed to document decreased glucose uptake in either type-1 (33) or type-2 (34) diabetic patients, despite a reduced rate of whole body glucose uptake. Thus, skeletal muscle and heart insulin resistance do not seem to coexist. These findings do not exclude defects within successive steps of carbohydrate oxidation, which may limit the rate of glycolysis and the Krebs cycle in the diabetic heart. It has been found that insulin has an independent effect on lactate oxidation in the canine heart, suggesting the direct activation of pyruvate dehydrogenase (35). Ferrannini et al. (16) observed in humans that physiological hyperinsulinemia increases the heart's lactate extraction rate more than two-fold. Based on these data, a defect of pyruvate dehydrogenase may be hypothesized in the diabetic heart, and the cardiac insulin resistance may be suggested as a possible background factor for the development of the "diabetic cardiomyopathy" in type-2 diabetes.

In conclusion, our study is the first to show that supra-physiological levels of circulating insulin in normal humans do not modify LVEF at rest, but significantly increase it in response to a submaximal work, as assessed by radionuclide ventriculography. In noninsulin-dependent diabetic subjects, this increment also occurs at rest, even when both rest and stress-LVEF appear to be significantly lower in this population than it is healthy subjects. Further investigations need to interpret the physiological mechanisms and significance of the synergy between exercise and insulin on LVEF and confirm the eventual relationship between insulin resistance in the heart and the left ventricular systolic hypofunction in NIDDM.

REFERENCES

1. Lee JC, Downing SE. Effects of insulin on cardiac muscle contraction and responsiveness to norepinephrine. Am J Physiol 1976;230:1360–5.
2. Downing SE, Lee JC. Myocardial and coronary vascular responses to insulin in the diabetic lamb. Am J Physiol 1979;237:H514–9.
3. Whitlow PL, Rogers WJ, Smith LR, et al. Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. Am J Cardiol 1982;49:811–20.
4. Fisher BM, Gillen G, Dargie HJ, et al. The effects of insulin-induced hypoglycemia on cardiovascular function in normal man: studies using radionuclide ventriculography. Diabetologia 1987;30:841–5.
5. Avasthi PS, Greene ER, Voyles WF. Noninvasive Doppler assessment of human postprandial renal blood flow and cardiac output. Am J Physiol 1987;252:F1167–74.
6. Baron AD, Brechtel G. Insulin differentially regulates systemic and skeletal muscle vascular resistance. Am J Physiol 1993;265:E61–7.
7. Baron AD, Laakso M, Brechtel G, et al. Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. J Clin Endocrinol Metab 1990;70:1525–33.
8. Bruce RA. Exercise testing of patients with coronary heart disease. Ann Clinical Res 1971;3:323–32.
9. Ziegler D, Laux G, Dannehl K, et al. Assessment of cardiovascular function: age related normal ranges and reproducibility of spectral analysis, vector analysis and standard tests of heart rate variation and blood pressure responses. Diabet Med 1992;9:166–75.
10. Raev D. Left ventricular function in young cardiac-asymptomatic type I (insulin-dependent) diabetics. Academic dissertation. Stara Zagora, Stara Zagora Medical University, 1992.
11. Bacharach SL, Green MV, Borer JS, et al. A real-time system for multi-image gated cardiac studies. J Nucl Med 1997;18:79–84.
12. Borer JS, Bacharach SL, Green MV, et al. Assessment of ventricular function by radionuclide angiography: applications and results. Cardiology 1984;71:136–61.
13. Massardo T, Gal RA, Grenier RP, et al. Left ventricular volume calculation using a count-based ratio method applied to multigated radionuclide angiography. J Nucl Med 1990;31:450–6.
14. Salvatore T, Cozzolino D, Giunta R, et al. Decreased insulin clearance as a feature of essential hypertension. J Clin Endocrinol Metab 1992;74:144–9.
15. Airaksinen J, Lahtela JT, Ikäheimo MJ, et al. Intravenous insulin has no effect on myocardial contractility or heart rate in healthy subjects. Diabetologia 1985;28:649–52.
16. Ferrannini E, Santoro D, Bonadonna R, et al. Metabolic and hemodynamic effects of insulin on human hearts. Am J Physiol 1993;264:E308–15.
17. Baron AD. Hemodynamic actions of insulin. Am J Physiol 1994;267:H187–E202.
18. Uusitupa M, Mustonen J, Laasko M, et al. Impairment of diastolic function in middle-aged type 1 and type 2 diabetic patients free of cardiovascular disease. Diabetologia 1988;31:783–91.
19. Di Bonito P, Cuomo S, Moio N, et al. Diastolic dysfunction in patients with noninsulin-dependent diabetes mellitus of short duration. Diabet Med 1996;13:321–4.
20. Celentano A, Vaccaro O, Tammaro P, et al. Early abnormalities of cardiac function in noninsulin-dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 1995;76:1173–8.
21. Lucchesi BR, Medina M, Kniffen FJ. The positive inotropic action of insulin in the canine heart. Eur J Pharmacol 1972;18:107–15.
22. Schaible TF, Malhotra A, Bauman WA, Scheuer J. Left ventricular function after chronic insulin treatment in diabetic and normal rats. J Mol Cell Cardiol 1983;15:445–58.
23. Regan TJ, Frank MJ, Lehan PH, Hellems HK. Relationship of insulin and strophanthidin to myocardial metabolism and function. Am J Physiol 1963;205:790–4.
24. Bing RJ, Siegel A, Vitale A, et al. Metabolic studies on the human heart in vivo. Am J Med 1953;15:284–96.
25. Neely JR, Morgan HE. Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle. Annu Rev Physiol 1974;36:413–59.
26. Heiss HW, Barmeyer J, Keul J, Reindell H. Myocardial oxygen consumption and substrate uptake in man during physiological and pathological volume load. Basic Res Cardiol 1977;72:293.
27. Wisneski JA, Stanley WC, Neese RA, Gertz EW. Effects of acute hyperglycemia on myocardial glycolytic activity in humans. J Clin Invest 1990;85:1648–56.

28. Lopaschuk GD, Collins-Nakai RL, Itoi T. Developmental changes in energy substrate use by the heart. Cardiovasc Res 1992;26:1172–80.
29. Camici P, Marraccini P, Marzilli M, et al. Coronary hemodynamics and myocardial metabolism during and after pacing stress in normal humans. Am J Physiol 1989;257:E309–17.
30. Young JL, Burr IM, Perry JM, et al. Inotropic effect of tolbutamide in man. Am Heart J 1975;89:189–94.
31. Schaffer SW, Seyed-Mozaffari M, Cutcliff CR, Wilson GL. Postreceptor myocardial metabolic defect in a rat model of noninsulin-dependent diabetes mellitus. Diabetes 1986;35:593–7.
32. Schaffer SW, Wilson GL. Insulin resistance and mechanical dysfunc-tion in hearts of Wistar rats with streptozotocin-induced noninsulin-dependent diabetes mellitus. Diabetologia 1993;36:195–9.
33. Nuutila P, Knuuti J, Ruotsalainen U, et al. Insulin resistance is localized to skeletal but not heart muscle in type 1 diabetes. Am J Physiol 1993;264:E756–62.
34. Voipio-Pulkki LM, Nuutila P, Knuuti J, et al. Heart and skeletal muscle glucose disposal in type-2 diabetic patients as determined by positron emission tomography. J Nucl Med 1993;34:2064–7.
35. Young LH, Zaret BL, Barrett EJ. Physiologic hyperinsulinemia stimulates lactate extraction by heart muscle in the conscious dog. Metab Clin Exp 1989;38:1115–9.