Independent Association of Type 2 Diabetes and Coronary Artery Disease With Myocardial Insulin Resistance

Patricia Iozzo,[1,2] Panithaya Chareonthaitawee,[1] David Dutka,[1] D. John Betteridge,[3] Ele Ferrannini,[2] and Paolo G. Camici[1]

Clustering of classical cardiovascular risk factors is insufficient to account for the excess coronary artery disease (CAD) of patients with diabetes, and chronic hyperglycemia and insulin resistance (IR) are obvious culprits. Whole-body and skeletal muscle IR is characteristic of patients with type 2 diabetes, but whether it extends to the normally contracting cardiac muscle is controversial. We investigated whether type 2 diabetes is associated with myocardial IR independent of CAD in a case-control series (n = 55) of male nondiabetic and diabetic (type 2 and type 1) patients with or without angiographically documented CAD. Baseline blood flow (^{15}O-water) and insulin-stimulated glucose uptake (^{18}F-fluoro-deoxyglucose) during euglycemic (5.6 mmol/l), physiological hyperinsulinemia (40 mU · min^{-1} · m^{-2} insulin clamp) were measured by positron emission tomography in skeletal muscle and normally contracting myocardium. Skeletal muscle glucose uptake was reduced in association with both CAD and type 2 diabetes. In regions with normal baseline perfusion, insulin-mediated myocardial glucose uptake was reduced in non-CAD type 2 diabetic (0.36 ± 0.14 μmol · min^{-1} · g^{-1}) and nondiabetic CAD patients (0.44 ± 0.15 μmol · min^{-1} · g^{-1}) in comparison with healthy control subjects (0.61 ± 0.08) or with non-CAD type 1 diabetic patients (0.80 ± 0.13; P < 0.001 for both CAD and diabetes). Neither basal skeletal muscle nor basal myocardial blood flow differed across groups; both skeletal muscle and myocardial IR were directly related to whole-body IR. We conclude that type 2 diabetes is specifically associated with myocardial IR that is independent of and nonadditive with angiographic CAD and proportional to skeletal muscle and whole-body IR. *Diabetes* 51:3020–3024, 2002

From the [1]Medical Research Council Clinical Sciences Centre, Faculty of Medicine, Imperial College of Science, Technology and Medicine, Hammersmith Hospital, London, U.K.; the [2]National Research Council Institute of Clinical Physiology and Department of Internal Medicine, University of Pisa School of Medicine, Pisa, Italy; and the [3]Department of Medicine, University College of London, Middlesex Hospital, London, U.K.

Address correspondence and reprint requests to Paolo G. Camici, MD, MRC Clinical Sciences Centre, Hammersmith Hospital, Du Cane Road, W12 ONN London, U.K. E-mail: paolo.camici@csc.mrc.ac.uk.

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CAD, coronary artery disease; FDG, ^{18}F-fluoro-deoxyglucose; FFA, free fatty acid; IR, insulin resistance; M, whole-body glucose utilization; MBF, myocardial blood flow; MGU, myocardial glucose uptake; PET, positron emission tomography; SBF, skeletal muscle blood flow; SGU, skeletal muscle glucose uptake.

The adverse cardiovascular prognosis associated with diabetes has not been fully explained (1). Clustering of classical cardiovascular risk factors is insufficient to account for the excess coronary artery disease (CAD) of patients with diabetes, and chronic hyperglycemia and impaired insulin action seem to be obvious culprits. Normal myocardium derives most of its energy from free fatty acid (FFA) oxidation in the fasting state and from glucose oxidation in the fed state (2). During myocardial ischemia, downregulation of energy expenditure together with a shift toward anaerobic metabolism represents one first line of defense; in fact, intracellular availability of glucose seems to play a pivotal role in the recovery of contractile function after revascularization (2–4). In patients with CAD, the metabolic changes extend beyond the injured myocardium, as the ability of insulin to promote glucose metabolism in the unaffected, normally contracting myocardium—as well as at the whole-body level—is markedly impaired (5,6).

Diabetes is a widely recognized state of whole-body insulin resistance (IR). Few studies have assessed insulin-stimulated glucose metabolism in the myocardium of patients with diabetes. In patients with type 1 diabetes, myocardial insulin sensitivity has been repeatedly shown to be preserved (7,8). In individuals with type 2 diabetes, however, studies have yielded conflicting results. Ohtake et al. (9) reported insulin-stimulated glucose uptake to be slightly impaired in patients with type 2 diabetes without CAD. This finding was more recently confirmed by Yokoyama et al. (10). Voipio-Pulkki et al. (11) described the same phenomenon in patients with type 2 diabetes and CAD. In a subsequent publication (12), the same authors were unable to confirm their observation, the apparent contradiction being attributed to metabolic differences between study groups. More recently, Utriainen et al. (13) demonstrated that under conditions of supraphysiological insulinization, there is no reduction of ^{18}F-fluoro-deoxyglucose (FDG) accumulation in the myocardium of patients who have type 2 diabetes and are free of CAD.

The present study therefore was undertaken to explore the interaction of CAD with diabetes, type 1 or type 2, in the genesis of myocardial IR. We used positron emission tomography (PET) in combination with the euglycemic insulin clamp to quantify whole-body, skeletal, and myocardial glucose uptake (MGU) simultaneously under stan-

TABLE 1
Clinical characteristics of the study subjects

	CAD	Type 1 diabetic subjects	Type 2 diabetic subjects	Control subjects
n	17	6	18	14
Age	60 ± 10*	49 ± 12	62 ± 10*	49 ± 7
BMI (kg/m^2)	26.5 ± 2.4	27.3 ± 6.7	26.3 ± 2.8	25.3 ± 2.3
RPP (mmHg · bpm^{-1} · 10^{-3})	8.6 ± 2.5	8.2 ± 0.8	8.5 ± 1.8	8.2 ± 1.1
Ejection fraction (%)	35 ± 11*	48 ± 27	49 ± 16	61 ± 10
FPG (mmol/l)	5.7 ± 0.7	10.8 ± 3.9*	8.9 ± 3.8*	4.9 ± 0.7
Clamp [G] (mmol/l)	5.4 ± 0.7	5.9 ± 0.6	5.9 ± 1.3	5.2 ± 0.9

RPP, rate-pressure product; FPG, fasting plasma glucose concentration; clamp [G], steady-state glucose concentration during the insulin clamp. *$P < 0.05$ or less vs. control subjects.

dardized experimental conditions. Baseline, non–insulin-stimulated myocardial and skeletal muscle blood flow was also assessed by use of PET.

RESEARCH DESIGN AND METHODS

Subjects. The study was composed of 41 male patients and 14 healthy male volunteers; their clinical characteristics are given in Table 1. CAD patients had evidence of left ventricular dysfunction and were referred for a PET viability scan after diagnostic coronary angiography. All had at least one significant stenosis (>70% luminal diameter) subtending a dysfunctional but PET-viable region. However, they had at least one left ventricular region with normal contractility as evaluated by radionuclide ventriculography or echocardiography. Two patients with type 2 diabetes who had undergone previous triple bypass surgery and were symptom-free at the time of the study were still considered positive for CAD. Non-CAD nondiabetic subjects were policemen undergoing periodical medical screening, whereas non-CAD uncomplicated patients with diabetes were recruited from the outpatient diabetes clinic. Both had a negative history of cardiovascular disease, normal heart rate, normal blood pressure (mean ± SE: 130 ± 4/74 ± 2 and 134 ± 7/75 ± 3 mmHg, respectively; NS), and normal resting electrocardiogram and echocardiogram. None of the healthy control subjects was taking any medication or was participating in an intense physical training program at the time of the study. All subjects were asked to consume a diet containing at least 200 g of carbohydrate for 3 days before the study. The study was approved by the Research Ethics Committee of Hammersmith Hospital and by the U.K. Administration of Radioactive Substances Advisory Committee. All subjects gave written informed consent before the study.

PET scanning. Scans were performed using an ECAT 931-08/12 scanner (CTI, Knoxville, TN) with a 10.5-cm axial field of view and a resolution of 8.4 × 8.3 × 6.6 mm full width at half maximum (14,15). All studies were conducted after a 10- to 12-h fast. After optimization of patient position, a 20-min transmission scan was performed after exposure of a retractable ^{68}Ge ring source to correct all subsequent emission data for tissue attenuation of γ photons. Then, ^{15}O-labeled carbon monoxide was administered by inhalation, and a single-frame scan was performed to image the blood pool (5,6). After allowing 10 min for decay of ^{15}O radioactivity, ^{15}O-water (10.5 MBq/kg) was injected intravenously over 20 s at an infusion rate of 10 ml/min to measure myocardial blood flow (MBF), as previously described (16,17). A primed-continuous (40 mU · min^{-1} · m^{-2}) systemic infusion of insulin was started immediately after the ^{15}O-water scan, and a 150-min euglycemic-hyperinsulinemic clamp was carried out (18). Euglycemia was maintained using a 20% dextrose infusion adjusted according to frequent plasma glucose measurements. In patients who had diabetes and presented with fasting hyperglycemia, the glucose infusion was not started before euglycemia was achieved. After 90 ± 10 min had elapsed from the start of the clamp, FDG (185 MBq) was infused over 2 min and a dynamic scan was carried out as described previously (5,6) for the measurement of MGU and skeletal muscle glucose uptake (SGU).

Plasma glucose was measured by the glucose oxidase technique (on a Beckman Glucose Analyzer; Beckman, Fullerton, CA), and plasma samples were frozen at −20°C for later insulin and FFA assay. Plasma insulin (Linco Research, St. Charles, MO) was assayed by a specific radioimmunoassay. Serum FFAs were measured spectrophotometrically (Wako, Neuss, Germany).

Image processing. All sinograms were corrected for tissue attenuation and reconstructed through standard reconstruction algorithms. Image manipulation and data handling were performed on SUN SPARC 2 and ULTRA 10 workstations (Sun Microsystems, Mountain View, CA) as previously described (5,6,17) with the use of Matlab software package (The MathWorks, Natick, MA).

Regions of interest. All images were resliced along the short axis, and the free wall of the left ventricle was divided according to the 16-segment model recommended by the American Society of Echocardiography (19,20). Regions of interest were drawn on the short-axis images on a plane-by-plane basis as described (20).

Regions of interest for SGU and skeletal muscle blood flow (SBF) measurements were placed on the medial portion of the left arm, contralateral to FDG and insulin injection site. Choice of the arm muscle instead of the leg, as used by other authors (7,11,13), was uniquely based on the advantage that this muscle lies within the same field of view as the myocardium and can be scanned simultaneously.

Data analysis. MGU, MBF, SGU, and SBF were quantified as previously described (5,6,17). Only myocardial regions with normal contractility were included in the analyses. Lumped constant values of 1.0 and 1.2 were used to derive MGU (21,22) and SGU (23–25), respectively. MGU was corrected for partial volume effect (5,6). Whole-body glucose utilization (M) was computed during the steady-state phase of the clamp.

Statistical analysis. Data are presented as mean ± SD. One-way ANOVA with Bonferroni-Dunn post hoc analysis was used for group comparisons. To test for the independent effect of type of diabetes and presence of CAD on metabolic variables while accounting for confounders, we set up mixed multivariate models, with age and BMI as continuous variables and diabetes (type 1 or type 2) and CAD as categorical factors. In these models, interactions between any two specified factors were also calculated.

RESULTS

Patients with type 2 diabetes and nondiabetic CAD subjects were older than patients with type 1 diabetes and healthy control subjects ($P < 0.01$); BMI was not significantly different across groups. Fasting plasma glucose concentrations were higher in patients with than without diabetes ($P < 0.01$), but glucose levels were held at similar steady-state values during the insulin clamp (Table 1). The ejection fraction ($n = 40$) was selectively reduced in association with CAD ($P < 0.0001$ after adjusting for age, BMI, and diabetes status). In a subset of subjects (seven healthy controls and nine patients with type 2 diabetes), plasma FFA levels were comparable at baseline (1.00 ± 0.30 vs. 0.88 ± 0.22 mEq/l, respectively; NS) and were equally suppressed during the clamp (0.34 ± 0.27 vs. 0.22 ± 0.09 mEq/l, respectively; NS); plasma insulin levels averaged 23 ± 7 and 378 ± 34 pmol/l at baseline and during the clamp, respectively, with no differences between control subjects and patients with diabetes.

PET measurements. Both M and MGU were reduced in CAD patients whether they had type 1, type 2, or no diabetes. In addition, M and MGU were reduced in association with type 2 diabetes but not type 1 diabetes (Table 2). Likewise, SGU was decreased in association with both CAD and type 2 diabetes, independent of one another. For both M and MGU, a significant ($P < 0.04$) negative interaction existed between CAD and type 2 diabetes, such that the reduction in MGU (or M) in patients with type 2

TABLE 2
Tissue blood flow and glucose uptake in cardiac and skeletal muscle

	CAD	T1D,CAD$^+$	T2D,CAD$^+$	T1D,CAD$^-$	T2D,CAD$^-$	Control subjects	*P** T2D	*P** CAD
M (μmol · min^{-1} · kg FFM^{-1})	24.9 ± 10.4	23.7 ± 11.7	20.3 ± 11.3	37.4 ± 3.8	22.1 ± 11.1	41.4 ± 15.7	0.004	0.001
MGU (μmol · min^{-1} · g^{-1})	0.44 ± 0.15	0.49 ± 0.16	0.34 ± 0.13	0.80 ± 0.13	0.36 ± 0.14	0.61 ± 0.08	0.0006	0.0008
MBF (ml · min^{-1} · g^{-1})	0.84 ± 0.19	1.09 ± 0.27	0.91 ± 0.20	1.20 ± 0.09	0.83 ± 0.029	1.07 ± 0.16	NS	NS
SGU (μmol · min^{-1} · g^{-1})	0.023 ± 0.011	0.017 ± 0.001	0.020 ± 0.007	0.036 ± 0.006	0.028 ± 0.012	0.037 ± 0.017	0.06	0.0009
SBF (ml · min^{-1} · g^{-1})	0.037 ± 0.014	0.031	0.046 ± 0.025	0.038 ± 0.013	0.058 ± 0.016	0.050 ± 0.019	NS	NS

T1D, type 1 diabetes; T2D, type 2 diabetes; with (CAD$^+$) or without CAD (CAD$^-$). **P* value for the independent effect of type 2 diabetes and CAD adjusted for age and BMI.

diabetes and CAD was less than the sum of decrements associated with each abnormality alone (Fig. 1). In the whole data set, age was not a significant correlate of either MGU or SGU. Neither MBF nor SBF differed significantly across study groups when age and BMI were adjusted for.

Both MGU and SGU were positively related to M (Fig. 2). Moreover, a direct relationship was found to exist between MGU and the ejection fraction (Fig. 3). By multivariate analysis of the whole data set, both M and MGU were reciprocally related to BMI (partial $r = 0.34$ and 0.36, respectively; both $P = 0.01$ after controlling for age, CAD, and type of diabetes), whereas fasting plasma glucose concentrations were unrelated to M or MGU.

DISCUSSION

The salient finding of the present study is that type 2 diabetes is associated with severe myocardial IR regardless of CAD and despite normal basal blood flow. In normally contracting myocardium, insulin-mediated glucose uptake was found to be reduced by 41% in patients with type 2 diabetes and no clinical evidence of cardiovascular disease as compared with nondiabetic control subjects; this reduction could not be ascribed to differences in BMI or age. It is interesting that myocardial IR was similar in patients with type 2 diabetes with or without CAD (Fig. 1).

The present study was designed to resolve the controversy concerning the integrity of insulin action in the myocardium of patients with diabetes. Previous studies have been partly conducted on the "normal" myocardium of patients with CAD and concomitant diabetes (11,12). As CAD is by itself associated with myocardial and whole-body IR (5,6), extrapolation of those findings to the myocardium of patients with type 2 diabetes without CAD is not justified. Moreover, differences in glucose and insulin infusion protocols have resulted in inhomogeneous data both within and between studies (9–13), and in none of the previous studies was blood flow measured. The current study overcomes most of the above limitations:

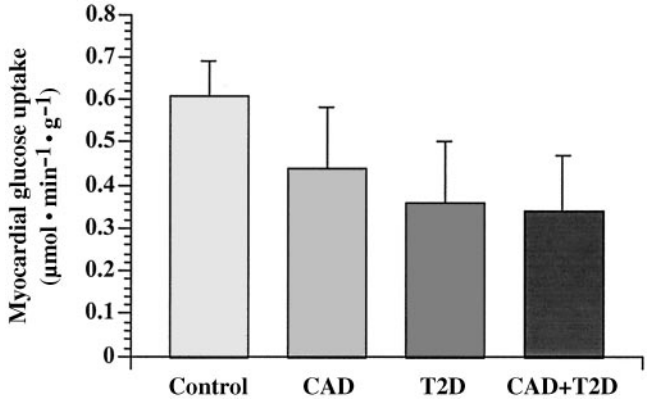

FIG. 1. Insulin-mediated MGU in healthy (nondiabetic, non-CAD) subjects, in nondiabetic patients with CAD, in non-CAD patients with type 2 diabetes (D2), and in patients with type 2 diabetes and CAD (the statistical analysis of these data are given in Table 2).

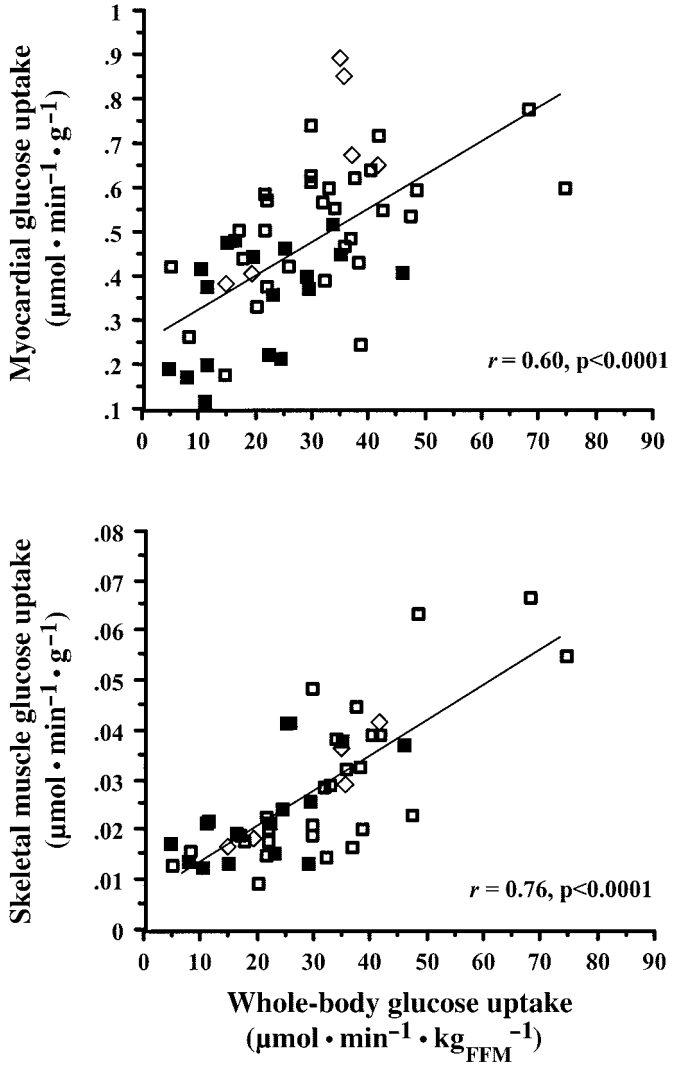

FIG. 2. Direct relationship between myocardial muscle (top) and skeletal muscle (bottom) insulin-mediated glucose uptake and whole-body glucose disposal in the whole study group. □, control subjects; ◇, type 1 diabetic subjects; ■, type 2 diabetic subjects.

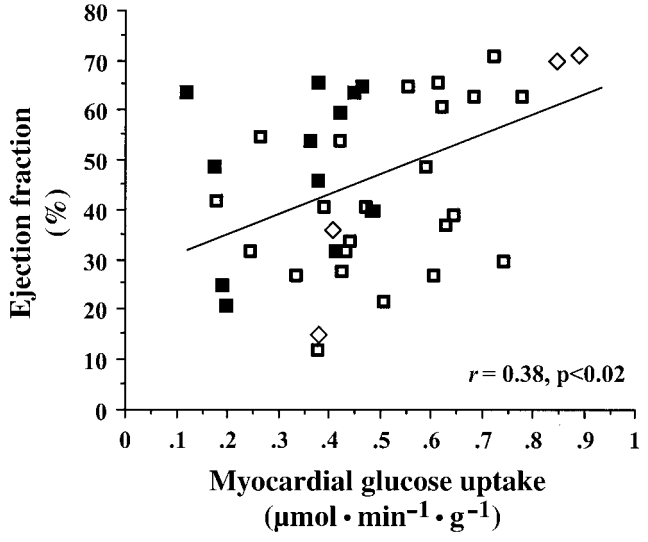

FIG. 3. Direct relationship between the ejection fraction and myocardial muscle insulin-mediated glucose uptake. □, control subjects; ◇, type 1 diabetic subjects; ■, type 2 diabetic subjects.

the pertinent spectrum of clinical combinations was included; the assessment of glucose uptake was performed under uniform experimental conditions of euglycemia and physiological hyperinsulinemia; and baseline blood flow was measured, proving that MGU results pertained to segments of the heart with a normal resting perfusion.

Our results are in agreement with those reported by Ohtake et al. (9), Voipio-Pulkki et al. (11), and, most recently, by Yokoyama et al. (10). The impairment of insulin-mediated myocardial glucose disposal reported by these authors in patients with type 2 diabetes ranges between 22 and 39%. Utriainen et al. (13), conversely, found comparable rates of MGU in patients with type 2 diabetes and healthy control subjects under conditions of supraphysiological insulinization (200 mU $\cdot$ min^{-1} $\cdot$ m^{-2} insulin clamp) and after an overnight insulin infusion in the patients with diabetes alone. Although we cannot exclude that pharmacological insulin stimulation might overcome the defect observed in our patients, the present study clearly demonstrates that cardiac glucose uptake in response to physiological hyperinsulinemia is defective in type 2 diabetes. Basal MBF was found to be similar across study groups, which is compatible with the fact that only regions with normal contractility were included in the present study and tended to be higher in patients with type 1 diabetes, an observation that has been previously reported (26).

The current findings convey a dual implication. First, because survival of myocytes after exposure to an ischemic insult seems to be dependent, at least in part, on the intrinsic ability of these cells to extract and metabolize glucose (3,27), the presence of myocardial IR lessens the a priori chances of a successful defense. It is well-established that neither the excess prevalence of CAD in individuals with diabetes in comparison with the normal population nor the poorer prognosis can be fully accounted for by the high-risk profile that often accompanies the disease (28). Myocardial IR might contribute to the pathogenesis and/or the unfavorable outcome of CAD in patients with diabetes. Second, the assessment of glucose uptake with PET is a reliable indication of the viability of dysfunctional myocardium in patients with CAD (3,27), such that this test has become a cornerstone in the medical and surgical treatment of these patients. On the basis of the current findings, defective MGU may be unrelated to clinically detectable CAD in patients with type 2 diabetes. Therefore, any reference criterion or threshold derived from a "normal" population may not be directly applicable to individuals with diabetes.

The current study confirms that CAD is accompanied by a generalized state of IR, which involves in a similar degree the whole-body, skeletal muscle, and normally contracting myocardium (5). In a similar manner but to a more severe extent, the impairment of insulin action in patients with type 2 diabetes seems to involve all target tissues. In line with the literature, no difference in glucose uptake was detected between patients with type 1 diabetes and individuals without diabetes. Our results extend previous findings by showing that type 2 diabetes and CAD do not induce additive impairment in insulin action. This suggests that at least one intracellular step is involved in common between the two conditions or that once the defect has reached a certain degree of severity, it cannot be further affected. More important, our data suggest that IR at the level of the myocardium may antedate and, possibly, cause the development of CAD. Thus, the biological background for the excess CAD found in type 2 diabetes may be established by the decades of IR that accompany diabetes from the prediabetic stage into the hyperglycemic phase (29).

Hyperglycemia is a widely recognized cause of IR in skeletal muscle (30,31), and raised plasma glucose concentrations even within the nondiabetic range have been associated with a higher cardiovascular risk (32). In the present study group, the broad range of basal plasma glucose levels made it possible to explore the short-term contribution of fasting glycemia to insulin-mediated glucose uptake in the myocardium. We found no independent relationship between the severity of hyperglycemia and myocardial IR or MBF. As glycosylated hemoglobin concentrations or chronic glycemic control were not measured in our subjects, extrapolation of this finding to chronic hyperglycemia cannot be made. The relationship between chronic hyperglycemia and myocardial insulin sensitivity might deserve further investigation, especially in patients with type 1 diabetes, in whom we and others (7,8) have been unable to detect any derangement. IR usually extends to the antilipolytic effect of insulin, resulting in inappropriately elevated plasma FFA concentrations, which competitively modulate myocardial glucose utilization (33,34). In the present study, we measured (in a subset of patients) plasma FFA in the fasting state and during the clamp but could not account for the differences in MGU on the basis of the circulating levels of this substrate.

Finally, we found a weak but significant correlation between ejection fraction and myocardial insulin sensitivity (Fig. 3). It has been argued that once CAD has been established, ensuing heart failure together with the consequent neurohormonal response and sedentary lifestyle may downregulate insulin action (35,36). It should be pointed out, however, that the impairment of MGU may

itself compromise myocardial performance. With time, a vicious circle may set in between defective glucose metabolism and inefficient contractility.

In summary, our data provide evidence that myocardial IR is an inherent feature of type 2 diabetes but not of type 1 diabetes. Consequently, a dedicated reference range for viability should be established in this population. In type 2 diabetes, myocardial IR is independent of CAD but not additive to it, suggesting shared pathogenetic mechanisms. In the natural history of type 2 diabetes, myocardial IR may be one of the causal factors in the development of CAD and heart failure.

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