Effects of Treatment With Sulfonylurea Drugs or Insulin on Ischemia-Induced Myocardial Dysfunction in Type 2 Diabetes

Roldano Scognamiglio,[1] Angelo Avogaro,[2] Saula Vigili de Kreutzenberg,[2] Christian Negut,[1] Monica Palisi,[1] Eros Bagolin,[2] and Antonio Tiengo[2]

In patients with diabetes and coronary artery disease, the potential negative role of sulfonylurea drugs is under intensive investigation. We assessed the effects of treatment with glibenclamide or insulin on the extension of left ventricular myocardial dysfunction induced by acute ischemia. Nineteen consecutive patients with type 2 diabetes and coronary artery disease entered the study. Each patient was randomly assigned to either insulin or glibenclamide therapy. Treatment was crossed over after 12 weeks and maintained for another 12 weeks. At the end of each treatment, left ventricular myocardial function at rest and during dipyridamole infusion was studied by two-dimensional echocardiography under the same conditions of metabolic control. Glibenclamide or insulin treatment did not influence the rest values of left ventricular dimensions, left ventricular ejection fraction (LVEF), or wall motion score index (WMSI). Dipyridamole infusion, in patients receiving glibenclamide treatment, decreased LVEF (43 ± 7 vs. 37 ± 12%, $P < 0.005$) and increased WMSI (1.4 ± 0.28 vs. 1.98 ± 0.24, $P < 0.001$) compared with baseline values; during insulin treatment, LVEF (46 ± 8 vs. 45 ± 11%, NS) and WMSI (1.4 ± 0.29 vs. 1.6 ± 0.4, NS) did not change significantly. Peak stress LVEF was higher (45 ± 11 vs. 37 ± 12%, $P < 0.001$) and WMSI lower (1.6 ± 0.4 vs. 1.98 ± 0.24, $P < 0.001$) in patients receiving insulin. The results indicate that in patients with type 2 diabetes and coronary artery disease, ischemic myocardial dysfunction induced by dipyridamole infusion is less severe during treatment with insulin than with glibenclamide. Restitution of a preconditioning mechanism in insulin-treated patients may be the potential beneficial mechanism. *Diabetes* 51:808–812, 2002

From the [1]Division of Cardiology, Department of Clinical and Experimental Medicine, University of Padua Medical School, Padua, Italy; and the [2]Division of Metabolic Diseases, Department of Clinical and Experimental Medicine, University of Padua Medical School, Padua, Italy.

Address correspondence and reprint requests to Roldano Scognamiglio, MD, Divisione di Cardiologia, Policlinico Universitario, via Giustiniani 2, 35128 Padua, Italy. E-mail: rscognamiglio@unipd.it.

Received for publication 4 June 2001 and accepted in revised form 29 November 2001.

3-BOH, 3-hydroxybutyrate; AcAc, acetoacetate; ECG, electrocardiogram; FFA, free fatty acid; IC_{50}, half-maximal inhibitory concentration; K_{ATP}, ATP-sensitive K^+ channel; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.

Patients with diabetes have a more than threefold increased risk of coronary ischemic events and congestive heart failure (1,2), as well as an increased incidence of late complications and increased mortality after acute myocardial infarction and coronary angioplasty (3–6). In patients with type 2 diabetes and myocardial ischemia, the use of sulfonylurea drugs may be harmful by preventing endogenous cardioprotective mechanisms to act. Ischemic preconditioning is a powerful, endogenous mechanism by which the myocardium may protect itself from ischemic insult, markedly reducing the impact of prolonged ischemia (7,8). In particular, in the human heart, preconditioning is able to reduce the severity of myocardial dysfunction associated with ischemia induced by coronary angioplasty, intermittent aortic cross-clamping during coronary artery bypass graft surgery, and exercise testing (9–11). In contrast, loss of preconditioning response has consistently been observed in the presence of sulfonylurea drugs (12,13). Inhibition of a metabolism-sensitive channel (ATP-sensitive K^+ channel [K_{ATP} channel]) present in both pancreatic β-cells (14) and cardiac myocytes (15) is the mechanism by which the sulfonylurea drugs cause ischemic preconditioning loss.

In this study, we assessed the effects of treatment with sulfonylurea drugs or insulin on sensitivity to ischemia and on the extension of ischemia-induced contractile dysfunction during dipyridamole stress echocardiography in patients with type 2 diabetes associated with ischemic heart disease.

RESEARCH DESIGN AND METHODS

Study patients. We studied 19 consecutive type 2 diabetic patients (15 men, 4 women, aged 61 ± 2 years [mean ± SD]) treated with diet plus oral sulfonylurea drugs. The main demographic and clinical characteristics of the study population during glibenclamide or insulin therapy are summarized in Table 1.

All patients had a clinical history of stable angina pectoris (Canadian Cardiovascular Society class 1 or 2) and evidence of significant coronary vessel obstruction (≥70% lumenal diameter narrowing) by coronary angiography (12 patients had two-vessel and 7 had three-vessel disease). Five patients had histories and electrocardiogram (ECG) evidence of previous myocardial infarction (four anterior and one inferior). Patients were excluded for any of the following reasons: *1*) previous or ongoing insulin therapy; *2*) severe diabetes; *3*) diabetic proliferative retinopathy assessed by an experienced ophthalmologist; *4*) diabetic neuropathy assessed by autonomic neuropathy tests or diabetic nephropathy (creatinine >1.4 mg/dl); *5*) potential sources of gastrointestinal bleeding, anemias, and other endocrine or major

organ diseases; *6*) arterial systemic hypertension; and *7*) inadequate echocardiogram to assess wall motion and thickening in every left ventricular (LV) myocardial segment. Nitrates were the only drugs permitted to control ischemic symptoms in study patients and were withdrawn 12 h before stress echocardiographic studies.

The study protocol was approved by the local ethics committee of the University of Padua School of Medicine, and written informed consent was obtained from all participants after the nature of the procedure was explained.

Study design. Before entering the study, all patients underwent a 7-day washout period, during which diet was maintained but sulfonylurea drugs were discontinued. Subsequently, each patient was randomly assigned to either insulin (15–45 IU twice or three times per day; Novo Nordisk, Copenhagen) or glibenclamide (5–15 mg per day) treatment. After 12 weeks of treatment with insulin or glibenclamide, all participants were admitted to the ward in the morning after an overnight fast and were studied at their prevailing plasma glucose value, in stable cardiac conditions. All patients underwent a full medical history and physical examination. Body weight (kg) and height (m) were recorded conventionally, and BMI was calculated. Blood pressure was measured in the sitting position on the same arm by the same observer with a mercury sphygmomanometer (phase V for diastolic value), and the mean value of three consecutive measurements was used. A resting standard 12-lead ECG was recorded in each patient. A blood sample was collected for the plasma determinations of glycated hemoglobin (HbA_{1c}), glycemia, insulinemia, C-peptide, free fatty acids (FFAs), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and fibrinogen and the blood determination of 3-hydroxybutyrate (3-BOH), lactate, pyruvate, and acetoacetate (AcAc). Finally, a two-dimensional echocardiographic study at rest and during dipyridamole infusion was performed. After completion of these evaluations, each patient was crossed over to either insulin or glibenclamide treatment for an additional 12 weeks. The same demographic, cardiac, and biochemical examinations were performed after the second period of therapy. To avoid any possibility of metabolic control interfering with cardiac performance, during both treatments, we scrupulously sought to keep glycemic control constant by means of outpatient visits at 7-day intervals and home glucose monitoring. Concomitant treatment remained unchanged throughout the study. In addition, we recruited 10 healthy control subjects matched for sex (eight men, two women) and age (60 ± 4 years).

Biochemical assays. HbA_{1c} was determined by a chromatographic method. Plasma glucose was measured with a glucose oxidase method on a Beckman glucose analyzer (Fullerton, CA). Plasma free insulin and C-peptide concentrations were determined by standard radioimmunoassays. Plasma FFA concentrations were determined using a microenzymatic technique. Plasma total cholesterol, HDL cholesterol, and triglycerides were determined with enzymatic techniques. LDL cholesterol was calculated with the Friedewald formula. Blood 3-BOH, lactate, pyruvate, and AcAc were determined by fluorimetric techniques. Plasma fibrinogen was determined by a standard laboratory method.

Echocardiographic analysis. Echocardiographic examinations were performed with Hewlett-Packard Sonos 5500 echocardiographic equipment (Andover, MA). Echocardiographic studies were coded and read by two independent observers in a blinded manner, with no knowledge of the patient's identity or experimental condition. Echocardiographic analysis was performed using the digitized cine loop method (PreVue III System; Nova MicroSonics, Mahwah, NJ). Wall motion and myocardial thickening were analyzed by dividing the left ventricle into 16 segments, and a semiquantitative score system (1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia) was used (16). Wall motion was detected by examining echocardiographic images of the left ventricle obtained in the apical four- and two-chamber views and in the parasternal long- and short-axis views. LV wall motion was analyzed by repeated viewing. Rest wall motion was considered abnormal when asynergy was detected in at least two contiguous segments. A wall motion score index (WMSI) was derived for rest and dipyridamole echocardiograms for each patient. The wall motion score index was acquired by summation of individual segment scores divided by the number of interpreted segments. Agreement of interobserver analysis for segmental asynergy was seen in 98% of the visualized segments. Discrepancies were resolved by consensus.

LV volumes were calculated by an ellipsoid biplane area-length method (17). LV ejection fraction (LVEF) was derived as end-diastolic volume minus end-systolic volume divided by the end-diastolic volume. LV endocardial echocardiograms in the apical four- and two-chamber views, for a minimum of two to four cardiac cycles, were digitized at end-diastole (R wave peak) and end-systole (time of smallest cavity area) by two independent observers. A discrepancy of >10 ml for LV volume required the analysis of the echocardiographic tracing by a third observer. Agreement was achieved by consensus. Interobserver and intraobserver variability for LV area ($r = 0.96$ and $r = 0.98$, respectively) and for LV length ($r = 0.95$ and $r = 0.95$, respectively) was acceptable. The interstudy variability of LVEF was assessed by echocardiographic examination twice within a half-hour and calculated by averaging the absolute differences between the two measurements. Changes in LVEF were considered significant if they were outside the 95% confidence limit of interstudy variability.

Dipyridamole echocardiography. Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with a dipyridamole infusion of 0.56 mg/kg body wt over 4 min followed by 4 min of observation, then an infusion of 0.28 mg/kg over 2 min. The cumulative dose was therefore 0.84 mg/kg over 10 min. Two-dimensional echocardiograms were obtained continuously during and up to 10 min after dipyridamole administration. Test results were considered positive when the wall motion score increased by one grade or more at peak stress (e.g., a normal segment becoming hypokinetic, akinetic, or dyskinetic or a hypokinetic segment becoming akinetic or dyskinetic). Akinesia becoming dyskinesia was not considered a positive result, however, because the change may have been due to a passive stretching phenomenon rather than active ischemia.

Statistical analysis. Results are expressed as means ± SD. Multiple comparisons were performed by a two-way repeated-measurement ANOVA, followed by the Fisher protected least significant difference test. A P value ≤0.05 by the two-tailed test was considered to indicate statistical significance.

RESULTS

Baseline LV function. Baseline characteristics of study patients are shown in Table 1. Measurements of LV end-diastolic volume index (LVEDVI) (64 ± 9 ml/m^2, range 54–74) and LVEF (60 ± 9%, range 57–70) in the control group were used to determine the means and 95% confidence limits of normal values. Resting values of LV dimensions and function are listed in Table 2. In diabetic patients, no differences were detected in baseline LVEDVI (glibenclamide, 109 ± 20 ml/m^2; insulin, 109 ± 19 ml/m^2; NS) and LVEF (glibenclamide, 43 ± 7%; insulin, 46 ± 8%; NS) during both treatments; the baseline LVEDVI values were higher ($P < 0.005$) and LVEF lower ($P < 0.005$) than those of control subjects, regardless of treatment group. Heart rate and systolic and diastolic blood pressures did not differ between diabetic patients and control subjects, regardless of treatment group. Regional impairment of myocardial contractility in diabetic patients did not differ during treatment with glibenclamide or insulin; in fact, baseline LV WMSI was similar in diabetic patients during both treatment strategies (glibenclamide, 1.40 ± 0.29; insulin, 1.40 ± 0.28; NS).

Dipyridamole echocardiography. Changes in heart rate and systolic blood pressure during dipyridamole infusion were similar in both treatment groups of diabetic patients (Table 2). During glibenclamide treatment, peak stress LVEF decreased (43 ± 7 vs. 37 ± 12%; $P < 0.005$) (Fig. 1) and WMSI increased significantly (1.4 ± 0.28 vs. 1.98 ± 0.24; $P < 0.001$) (Fig. 2) in comparison to the baseline values; in patients treated with insulin, peak stress LVEF (46 ± 8 vs. 45 ± 11%; NS) (Fig. 1) and WMSI (1.4 ± 0.29 vs. 1.6 ± 0.4; NS) (Fig. 2) did not differ from baseline values. It was noted that during insulin treatment, patients had significant changes in peak stress LV function compared with values obtained during glibenclamide therapy: LVEF was higher (45 ± 11 vs. 37 ± 12%; $P < 0.001$) and WMSI lower (1.6 ± 0.4 vs. 1.98 ± 0.24; $P < 0.001$).

Metabolic parameters. As shown in Table 2, no changes were observed in short- or long-term metabolic control between the two treatments; furthermore, no changes were observed in intermediary metabolites or plasma lipid levels. Only FFAs were slightly higher during glibenclamide treatment, although the difference was not statistically significant.

TABLE 1
Main demographic and biochemical characteristics of the study population

	Glibenclamide	Insulin
Sex (M/F)	14/5	14/5
Age (years)	61 ± 7	61 ± 7
BMI (kg/m^2)	29.3 ± 3.4	29.4 ± 3.5
Weight/height	0.94 ± 0.05	0.94 ± 0.05
Fasting plasma glucose (mg/dl)	234 ± 67	212 ± 75
Fasting plasma insulin (μU/ml)	16.9 ± 13	24.6 ± 19
C-peptide (ng/ml)	2.8 ± 2.0	2.1 ± 2.6
HbA_{1c} (%)	9.5 ± 1.3	9.9 ± 1.5
Free fatty acids (μmol/l)	799.7 ± 348	617.2 ± 366
Total cholesterol (mg/dl)	252 ± 33	250 ± 38
HDL cholesterol (mg/dl)	44 ± 11	47 ± 11
LDL cholesterol (mg/dl)	168 ± 30	172 ± 33
Fibrinogen (mg/dl)	291 ± 75	316 ± 80
Blood lactate (mmol/l)	1.279 ± 0.582	1.224 ± 0.558
Blood pyruvate (mmol/l)	0.081 ± 0.028	0.073 ± 0.029
Blood 3-BOH (mmol/l)	0.101 ± 0.107	0.092 ± 0.179
Blood AcAc (mmo/l)	0.083 ± 0.060	0.086 ± 0.092

Data are mans ± SD. None of the differences between groups are statistically significant.

DISCUSSION

The major aim of this study was to assess the effects of either insulin or glibenclamide therapy on susceptibility to ischemia, in terms of extension of left ventricular myocardial dysfunction, during dipyridamole infusion in type 2 diabetic patients with coronary artery disease. Because metabolic control per se may deeply affect several variables of cardiac function such as substrate utilization (18), coronary blood flow reserve (19), and myocardial contractility (20), we meticulously ensured the same metabolic control under the two different treatments. This control was maintained weekly by modifying therapies according to each patient's home blood glucose monitoring (Table 1). This result allowed us to assess the effect of each treatment on cardiac function without the confounding consequences of different metabolic control levels.

TABLE 2
Results of dipyridamole stress echocardiography variables

	Glibenclamide	Insulin	*P*
Baseline			
HR (beats/min)	75 ± 5	70 ± 4	NS
SBP (mmHg)	143 ± 8	145 ± 9	NS
DBP (mmHg)	86 ± 10	89 ± 8	NS
LVEDVI (ml/m^2)	109 ± 20	109 ± 19	NS
LVESVI (ml/m^2)	63 ± 19	59 ± 18	NS
LVEF (%)	43 ± 7	46 ± 8	NS
LV WMSI	1.4 ± 0.28	1.4 ± 0.29	NS
Dipyridamole			
HR (beats/min)	89 ± 7	89 ± 11	NS
SBP (mmHg)	135 ± 9	130 ± 15	NS
DBP (mmHg)	82 ± 10	85 ± 8	NS
LVEDVI (ml/m^2)	122 ± 19	108 ± 18	0.025
LVESVI (ml/m^2)	77 ± 16	60 ± 18	0.04
LVEF (%)	37 ± 12	45 ± 11	<0.001
LV WMSI	1.98 ± 0.24	1.6 ± 0.40	<0.001

Data are means ± SD. DBP, diastolic blood pressure; HR, heart rate; LVESVI, left ventricular end-systolic volume-index; SBP, systolic blood pressure.

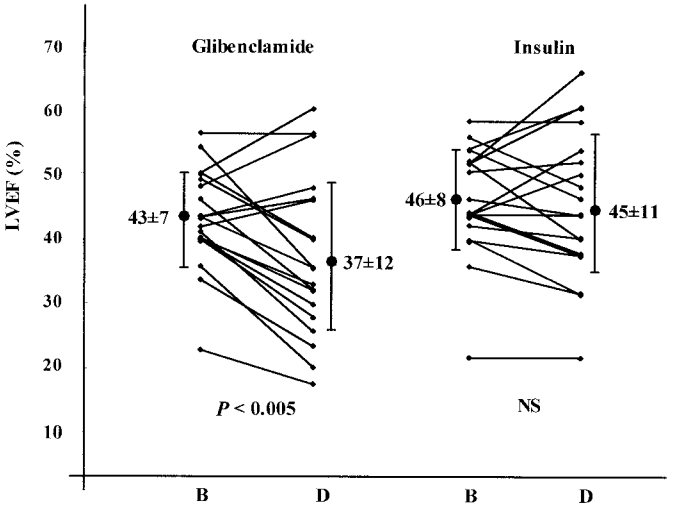

FIG. 1. Echocardiographic changes in LVEF induced by dipyridamole stress during glibenclamide or insulin treatment. B, baseline; D, dipyridamole.

In patients with type 2 diabetes, many factors contribute to increased morbidity and mortality by ischemic heart disease. One contributor may be the use of sulfonylurea drugs. Such a possibility, which first arose several years ago, has recently resurfaced after the discovery that sulfonylureas act by inhibiting K_{ATP} channels. In the heart, inhibition of these channels prevents ischemic preconditioning, an endogenous mechanism that protects the heart from ischemic injury. Furthermore, experimental data (21) suggest that the myocardium in streptozotocin-induced diabetic rat hearts may benefit more from preconditioning than normal myocardium, possibly as a result of the reduced production of glycolytic metabolites during sustained ischemia and the concomitant attenuation of intracellular acidosis.

The difficulty of translating these findings to the outcome of patients is demonstrated by some U.K. Prospective Diabetes Study data (22) that showed no increase in cardiovascular events with sulfonylurea drug use. On the

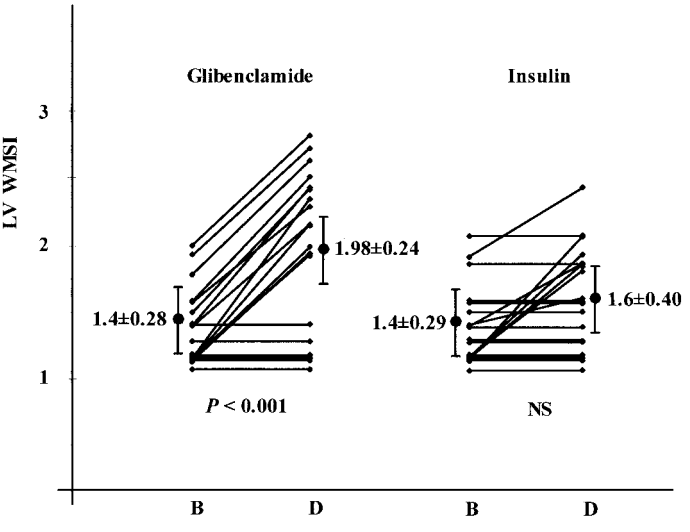

FIG. 2. Echocardiographic changes in LV WMSI induced by dipyridamole stress during glibenclamide or insulin treatment. B, baseline; D, dipyridamole.

other hand, in a recent prospective study (23), it has been shown that sulfonylurea drugs increased early mortality in patients with diabetes after direct angioplasty for acute myocardial infarction. However, the outcome of these patients may be influenced by several factors that could explain the controversies regarding long-term results; for example, angiotensin II type 1 receptor antagonists and ACE inhibitors are beneficial not only for suppressing ventricular remodeling (24) but also for preserving the preconditioning mechanism (25).

Our results reflect different effects of insulin and glibenclamide treatment on myocardial contractile function in patients with type 2 diabetes during acute ischemia provoked by dipyridamole infusion, and they should not be translated to other sulfonylurea drugs without further evidence. The diversities of sulfonylurea drugs relate to their potency and half-lives. However, there is increasing data to support that they may differ in their cardiovascular effects, possibly because of a distinct affinity for cardiac and vascular K_{ATP} channels. For example, the half-maximal inhibitory concentration (IC_{50}) of glimepiride in blood vessels has been reported to be 31.6 nmol compared with an IC_{50} of 6.8 nmol for glibenclamide. It should be noted, however, that these IC_{50} values are several orders of magnitude greater than the IC_{50} values for K_{ATP} channels in pancreatic islet cells. Plasma levels of glibenclamide in patients treated for type 2 diabetes range between 0 and 1.5 mmol/l. Because glibenclamide concentrations as low as 0.01 mmol/l have been shown to inhibit vascular relaxation induced by K_{ATP} channel–opening drugs, it is quite possible that significant vascular effects occur during glibenclamide treatment in type 2 diabetic patients (26). Moreover, in experimental and pharmacological studies, glibenclamide is used as a classical K_{ATP} channel inhibitor (27), and its deleterious effect on ischemic preconditioning has been widely investigated, suggesting a possible negative role in myocardial function in diabetic patients with coronary artery disease (27,28). Furthermore, glibenclamide is by far the most commonly used sulfonylurea drug for type 2 diabetes in Italy. For these reasons, and because of a more homogeneous effect using exclusively one instead of several different oral hypoglycemic agents, we decided to compare insulin versus glibenclamide. Further studies are needed to assess possible differences on the in vivo cardiac effects of other sulfonylurea drugs.

The results of this study show that ischemic myocardial dysfunction induced by dipyridamole infusion is more severe during treatment with sulfonylurea drugs than during insulin treatment of type 2 diabetic patients with documented ischemic heart disease. In fact, during glibenclamide treatment, peak stress LV global pump function (evaluated as ejection fraction) decreases and is significantly less than during insulin treatment. This impairment in LV systolic function is the result of an extension in ischemic myocardial dysfunction induced by dipyridamole, as demonstrated by the increase of LV WMSI. On the other hand, patients treated with insulin do not show a worsening of myocardial function during dipyridamole stress, as demonstrated by the absence of a significant increase in LV WMSI.

It is reasonable to suggest that the restitution of a preconditioning mechanism in insulin-treated patients is able to reduce the severity of myocardial dysfunction associated with ischemia induced by dipyridamole stress. Other possible mechanisms may be a locally higher plasma insulin concentration during insulin treatment causing *1*) an increase in coronary blood flow by a primary reduction in coronary tone secondary to insulin-mediated elaboration of vasoactive and/or paracrine factors within the coronary circulation (29) and *2*) a direct positive inotropic effect on postischemic heart, reducing the extension of myocardial dysfunction (30).

In this study, dipyridamole stress has been chosen for induction of myocardial ischemia on the basis of several considerations. It has been shown that dipyridamole is more effective, or at least no less effective, than dobutamine at producing flow disparity between myocardial regions supplied by normal and stenotic arteries (31–34). Moreover, minor and major complications appear more frequently during dobutamine than dipyridamole tests (33,34). On the other hand, the mechanism of action of dipyridamole renders this pharmacological stress particularly useful in the diabetic heart characterized by severe abnormalities in the coronary microcirculation and flow reserve along with the atherosclerotic occlusion of epicardial vessels. In fact, the standard dose of dipyridamole can induce maximal or near-maximal coronary vasodilatation in most patients (35), whereas dobutamine produces a significantly smaller increase in myocardial blood flow (36,37). Finally, the mechanism of action of dobutamine involves stimulation of cardiac adrenergic receptors. In the diabetic heart, a defective cardiac response to catecholamines occurs. This has been explained by an impairment of the cardiac adrenergic signaling system mainly due to the decrease in β-adrenergic receptor concentration (38–40).

Thus, this randomized crossover design study may help to define the potential negative action of glibenclamide in type 2 diabetic patients with coronary artery disease. The results demonstrate that ischemic myocardial dysfunction is easily inducible by dipyridamole in type 2 diabetic patients with ischemic heart disease. Insulin treatment instead of glibenclamide therapy significantly prevents this phenomenon. Although the precise underlying pathophysiological mechanism is not completely known, these data may eventually be important in designing optimal therapy for patients with type 2 diabetes.

REFERENCES

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
2. Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E, Pyorala K: Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
3. Mueller HS, Cohen LS, Braunwald E, Forman S, Feit F, Ross A, Schweiger M, Cabin H, Davison R, Miller D: Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction: analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation* 85:1254–1264, 1992
4. Granger CB, Califf RM, Young S, Candela R, Samaha J, Worley S, Kereiakes DJ, Topol EJ: Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. *J Am Coll Cardiol* 21:920–925, 1993
5. Stein B, Weintraub WS, Gebhart SP, Cohen Bernstein CL, Grosswald R, Liberman HA, Douglas JS Jr, Morris DC, King SB 3rd: Influence of diabetes

mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 91:979–989, 1995
6. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW: Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 94:1818–1825, 1996
7. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 74:1124–1136, 1986
8. Gross GJ: ATP-sensitive potassium channels and myocardial preconditioning. *Basic Res Cardiol* 90:85–88, 1995
9. Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW Jr, Herrmann HC, Laskey WK: Adaptation to ischemia during percutaneous transluminal coronary angioplasty: clinical, hemodynamic, and metabolic features. *Circulation* 82:2044–2051, 1990
10. Kloner RA, Yellon D: Does ischemic preconditioning occur in patients? *J Am Coll Cardiol* 24:1133–1142, 1994
11. Maybaum S, Ilan M, Mogilevsky J, Tzivoni D: Improvement in ischemic parameters during repeated exercise testing: a possible model for myocardial preconditioning. *Am J Cardiol* 78:1087–1091, 1996
12. Engler RL, Yellon DM: Sulfonylurea K_{ATP} blockade in type II diabetes and preconditioning in cardiovascular disease: time for reconsideration. *Circulation* 94:2297–2301, 1996
13. Cleveland JC Jr, Meldrum DR, Cain BS, Banerjee A, Harken AH: Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium: two paradoxes revisited. *Circulation* 96:29–32, 1997
14. Ashcroft SJ, Ashcroft FM: The sulfonylurea receptor. *Biochim Biophys Acta* 1175:45–59, 1992
15. Terzic A, Jahangir A, Kurachi Y: Cardiac ATP-sensitive K^+ channels: regulation by intracellular nucleotides and K^+ channel-opening drugs. *Am J Physiol* 269:C525–C545, 1995
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2:358–367, 1989
17. Wyatt HL, Heng MK, Meerbaum S, Gueret P, Hestenes J, Dula E, Corday E: Cross-sectional echocardiography. II. Analysis of mathematic models for quantifying volume of the formalin-fixed left ventricle. *Circulation* 61:1119–1125, 1980
18. Avogaro A, Nosadini R, Doria A, Fioretto P, Velussi M, Vigorito C, Sacca L, Toffolo G, Cobelli C, Trevisan R: Myocardial metabolism in insulin-deficient diabetic humans without coronary artery disease. *Am J Physiol* 258:E606–E618, 1990
19. Yokoyama I, Ohtake T, Momomura S, Yonekura K, Woo Soo S, Nishikawa J, Sasaki Y, Omata M: Hyperglycemia rather than insulin resistance is related to reduced coronary flow reserve in NIDDM. *Diabetes* 47:119–124, 1998
20. Schwingshandl J, Ward C, Silink M, Sholler G: Echocardiographic load-independent indices of contractility in children and adolescents with type I diabetes: effect of metabolic control and insulin on left ventricular performance. *Pediatr Cardiol* 16:1–5, 1995
21. Tatsumi T, Matoba S, Kobara M, Keira N, Kawahara A, Tsuruyama K, Tanaka T, Katamura M, Nakagawa C, Ohta B, Yamahara Y, Asayama J, Nakagawa M: Energy metabolism after ischemic preconditioning in streptozotocin-induced diabetic rat hearts. *J Am Coll Cardiol* 31:707–715, 1998
22. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group [published erratum appears in *Lancet* 352:1557, 1998]. *Lancet* 352:854–865, 1998
23. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr: Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 33:119–124, 1999
24. Schieffer B, Wirger A, Meybrunn M, Seitz S, Holtz J, Riede UN, Drexler H: Comparative effects of chronic angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor blockade on cardiac remodeling after myocardial infarction in the rat. *Circulation* 89:2273–2282, 1994
25. Miki T, Miura T, Tsuchida A, Nakano A, Hasegawa T, Fukuma T, Shimamoto K: Cardioprotective mechanism of ischemic preconditioning is impaired by postinfarct ventricular remodeling through angiotensin II type 1 receptor activation. *Circulation* 102:458–463, 2000
26. Howes LG: Cardiovascular effects of sulphonylureas: role of K_{ATP} channels. *Diabetes Obes Metab* 2:67–73, 2000
27. Gerich JE: Oral hypoglycemic agents. *N Engl J Med* 321:1231–1245, 1989
28. O'Rourke B: Myocardial K_{ATP} channel in preconditioning. *Circ Res* 87:845–855, 2000
29. McNulty PH, Pfau S, Deckelbaum LI: Effect of plasma insulin level on myocardial blood flow and its mechanism of action. *Am J Cardiol* 85:161–165, 2000
30. Doenst T, Richwine RT, Bray MS, Goodwin GW, Frazier OH, Taegtmeyer H: Insulin improves functional and metabolic recovery of reperfused working rat heart. *Ann Thorac Surg* 67:1682–1688, 1999
31. Mahmarian JJ: State of the art for coronary artery disease detection: thallium-201. In *Nuclear Cardiology: State of the Art and Future Directions*. Zaret BL, Beller GA, Eds., St. Louis, MO, Mosby, 1999, p. 237–272
32. Tadamura E, Iida H, Matsumoto K, Mamede M, Kubo S, Toyoda H, Shiozaki T, Mukai T, Magata Y, Konishi JU: Comparison of myocardial blood flow during dobutamine-atropine infusion with that after dipyridamole administration in normal men. *J Am Coll Cardiol* 37:130–136, 2001
33. Laine H, Raitakari OT, Niinikoski H, Pitkanen O-P, Iida H, Viikari J, Nuutila P, Knuuti J: Early impairment of coronary flow reserve in young men with borderline hypertension. *J Am Coll Cardiol* 32:147–153, 1998
34. Pitkanen OP, Nuutila P, Raitakari OT, Porkka K, Iida H, Nuotio I, Ronnemaa T, Viikari J, Taskinen M-R, Ehnholm C, Knuuti J: Coronary flow reserve in young men with familial combined hyperlipidemia. *Circulation* 99:1678–1684, 1999
35. Rossen JD, Quillen JE, Lopez AG, Stenberg RG, Talman CL, Winniford MD: Comparison of coronary vasodilation with intravenous dipyridamole and adenosine. *J Am Coll Cardiol* 18:485–491, 1991
36. Krivokapich J, Huang SC, Schelbert HR: Assessment of the effects of dobutamine on myocardial blood flow and oxidative metabolism in normal human subjects using nitrogen-13 ammonia and carbon-11 acetate. *Am J Cardiol* 71:1351–1356, 1993
37. Krivokapich J, Czernin J, Schelbert HR: Dobutamine positron emission tomography: absolute quantitation of rest and dobutamine myocardial blood flow and correlation with cardiac work and percent diameter stenosis in patients with and without coronary artery disease. *J Am Coll Cardiol* 28:565–572, 1996
38. Scognamiglio R, Avogaro A, Casara D, Crepaldi C, Marin M, Palisi M, Mingardi R, Erle G, Fasoli G, Dalla Volta S: Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 31:404–412, 1998
39. Severi S, Paterni M, Underwood R, Mohiaddin RH, Boyd H, Camici PG: Dobutamine stress: effects on regional myocardial blood flow and wall motion. *J Am Coll Cardiol* 26:1187–1195, 1995
40. Shigeta Y, Kashiwagi A: Pathophysiological mechanism of defective inotropic response to a β-adrenergic agonist in the diabetic heart. In *The Diabetic Heart*. Nagano M, Dhalla NS, Eds., New York, Raven Press, 1991, p. 35–44