Effect of Hypoglycemic Agents on Ischemic Preconditioning in Patients With Type 2 Diabetes and Symptomatic Coronary Artery Disease

Rosa Maria Rahmi, md, phd
Augusto Hiroshi Uchida, md, phd
Paulo Cury Rezende, md
Eduardo Gomes Lima, md
Cibele Larrosa Garzillo, md, phd
Desiderio Favarato, md
Celia M.C. Strunz, md, phd
Myrthes Takiuti, rn, phd
Priscyla Girardi, rn, phd
Whady Hueb, md, phd
Roberto Kalil Filho, md, phd
José A.F. Ramires, md, phd

OBJECTIVE—To assess the effect of two hypoglycemic drugs on ischemic preconditioning (IPC) patients with type 2 diabetes and coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS—We performed a prospective study of 96 consecutive patients allocated into two groups: 42 to group repaglinide (R) and 54 to group vildagliptin (V). All patients underwent two consecutive exercise tests (ET1 and ET2) in phase 1 without drugs. In phase 2, 1 day after ET1 and -2, 2 mg repaglinide three times daily or 50 mg vildagliptin twice daily was given orally to patients in the respective group for 6 days. On the seventh day, 60 min after 6 mg repaglinide or 100 mg vildagliptin, all patients underwent two consecutive exercise tests (ET3 and ET4).

RESULTS—In phase 1, IPC was demonstrated by improvement in the time to 1.0 mm ST-segment depression and rate pressure product (RPP). All patients developed ischemia in ET3; however, 83.3% of patients in group R experienced ischemia earlier in ET4, without significant improvement in RPP, indicating the cessation of IPC ($P < 0.0001$). In group V, only 28% of patients demonstrated IPC cessation, with 72% still having the protective effect ($P < 0.0069$).

CONCLUSIONS—Repaglinide eliminated myocardial IPC, probably by its effect on the K_{ATP} channel. Vildagliptin did not damage this protective mechanism in a relevant way in patients with type 2 diabetes and CAD, suggesting a good alternative treatment in this population.

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Ischemic preconditioning (IPC) is recognized as a protective endogenous mechanism by which brief and recurrent episodes of myocardial ischemia may self-protect from prolonged ischemic injury and, thus, limit the size of myocardial infarction (1). This mechanism can reduce the severity of myocardial ischemia associated with coronary angioplasty, intermittent aortic cross-clamping during coronary artery bypass graft surgery, and exercise testing (2). Subjects with chronic ischemic heart disease frequently describe angina provoked by an initial exercise and realize that the pain is attenuated and even disappears if they rest and restart the exercise. This phenomenon, called "warm-up" or "walk-through" angina, has been related to IPC and documented in a number of studies using serial exercise testing (3–8). The cellular pathways underlying IPC are not fully understood and are undoubtedly complex, involving triggers, mediators, memory, and end effectors. All steps appear to involve components, such as adenosine, adenosine receptors, the activation of K_{ATP} channel, and the ε-isoform of protein kinase C, as well as others, including the paradoxical protective role of oxygen radicals (9). The K_{ATP} channel opening in cardiac myocytes has consistently been observed to be important in contributing to protection from IPC (10).

Drugs that act by inhibiting K_{ATP} channels, such as some sulphonylureas, are related to loss of IPC (11–14). Tolbutamide and glibenclamide, drugs in the sulphonylurea family, promote additional binding to K_{ATP} channels with different molecular conformations in cardiac myocytes and vascular smooth muscle (sulphonylurea receptor [SUR]2A and SUR2B) and may contribute to adverse cardiovascular effects (11). On the other hand, newer sulfonylureas glimepiride and glicazide have a high affinity for SUR1, the pancreatic receptor, but low affinity for cardiac SUR2A or vascular SUR2B and, therefore, are able to maintain IPC (15–17).

Oral hypoglycemic agents remain a mainstay for the management of glycemic control in type 2 diabetes. Other agents besides sulfonylureas are used to treat type 2 diabetes, including repaglinide (R) (benzoic acid derivative) and dipeptidyl peptidase (DPP)-4 inhibitor drugs. R stimulates insulin secretion by binding to SUR1 in the plasma membrane of the β cell, although at a site distinct from the sulphonylurea binding site. It has been reported to inhibit the K_{ATP} channels of β cells, cardiomyocytes, and nonvascular smooth muscle cells with similar affinity, suggesting its effect on myocardium (18,19). Moreover, therapy with vildagliptin (V), a drug belonging to a class of DPP-4 inhibitors, is based on modulation of the incretin system. By inhibiting DPP-4, V prolongs the half-lives of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide—intestinal hormones that support glucose homeostasis and insulin secretion (20). GLP-1 is rapidly degraded by the enzyme DPP-4, which is widely expressed in many tissues, including kidney, liver, lung, and the small intestine. DPP-4 inhibitors exert their antidiabetes actions largely through potentiation of GLP-1 receptor (GLP-1R)

From the Department of Atherosclerosis, Heart Institute of the University of São Paulo, São Paulo, Brazil.
Corresponding author: Whady Hueb, mass@incor.usp.br.
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activation. The GLP-1Rs, G-protein–coupled receptors, are widely expressed in the pancreas, kidney, stomach, brain, lung, and heart (21). Studies with GLP-1R agonists have potential medical importance regarding the cardiovascular effects. In contrast, much less is known about the cardiovascular biology of DPP-4 and about cardiovascular outcomes with DPP-4 inhibitors. Moreover, inhibition of DPP-4 enzyme activity modulates the activity of cardioactive peptides such as brain natriuretic peptide, neuropeptide Y, and stromal cell–derived factor-1 via non–GLP-1 mechanisms of action (22). In this scenario, studies about the role of DPP-4 inhibitors on the cardiovascular system are critical. In this study, we assessed the effects of R and V on IPC, conducting a prospective study of type 2 diabetes and multivessel coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS

The study protocol was approved by the local ethics committee of the Hearth Institute of University of São Paulo. Written informed consent was obtained from all participants after the nature of the procedure was explained. All procedures were performed in accordance with the Declaration of Helsinki.

Patients with multivessel CAD (internal diameter reduction ≥70% of at least two major coronary branches), preserved left ventricular function, confirmed by transthoracic echodopplercardiography (left ventricular ejection fraction ≥50%), and type 2 diabetes presented by taking oral hypoglycemic drugs and documentation participated in this study. All patients had reproducible positive exercise tests for myocardial ischemia (horizontal or downsloping ST-segment depression ≥1.0 mm). No patients had evidence of left ventricular hypertrophy, myocardial infarction during the last 3 months, heart failure, cardiomyopathy, valvular disease, electrocardiogram changes, or conduction defects that could interfere with the interpretation of ST-segment changes. All patients had normal hepatic and renal function. Furthermore, oral hypoglycemic agents and cardiovascular drugs, including calcium channel and β-adrenergic blockers, ACE inhibitors, angiotensin II receptor blockers, and caffeine, were withdrawn 5 days before the study. Only nitrates were permitted in order to control ischemic symptoms, but they were withdrawn 12 h before consecutive treadmill exercise tests in phases 1 and 2. The main demographic, biochemical, and clinical characteristics of the study population are shown in Table 1.

This was a prospective, nonrandomized study. The patients were consecutively allocated to two groups: R and V groups with 42 and 54 patients, respectively. The R group was evaluated first as previously described (23), and the V group was evaluated second. The study was performed in two phases. Phase 1, without any drugs: All patients underwent two consecutive treadmill exercise tests (ET1 and ET2), with an interval of 30 min between to identify the ischemia and document the magnitude of IPC. In this phase, ET2 was aimed at assessing improvements in ischemic parameters. Phase 2, only hypoglycemic drugs (R or V): Oral R (2 mg three times daily) or V (50 mg twice daily) was given for 6 days. On the seventh day, 60 min after (time to peak plasma levels) 2 mg R or 100 mg V, all patients underwent two consecutive ETs (ET3 and ET4). The time interval between ET3 and ET4 was similar to that in phase 1. All tests were performed 1 h after lunchtime for avoidance of hypoglycemia.

Treadmill exercise testing

All patients underwent computer-assisted treadmill exercise tests, symptom limited, using the Bruce protocol, with a recovery phase of 6 min. The time interval between the consecutive tests was 30 min. We used a MAT2100 treadmill and a Fukuda Denshi ML8000 Stress Test system (Fukuda Denshi; Bunkyo-ku, Tokyo, Japan). A 12-lead electrocardiogram, heart rate, and arterial blood pressure were obtained with the patient in the standing position at baseline. A 12-lead electrocardiogram was also obtained at each 1.0-min interval during exercise, at peak exercise, each minute up to 6 min after the exercise phase, at the onset of 1.0-mm ST-segment depression, at major ST-segment deviation, at the onset of angina pectoris, and when it was clinically relevant. The electrocardiogram was continuously monitored during the exercise and recovery phases, and an up-to-date averaged electrocardiographic signal of all leads was continuously displayed on the computer screen. The level of the ST-segment deviation was based on visual analyses of the 0.08 s after the J point by two independent cardiologists in a blind fashion. In case of disagreement, a third cardiologist was consulted and the matter was resolved by consensus. Only the horizontal or downsloping ST-segment depressions were considered for the time to onset of 1.0-mm ST-segment depression evaluation (T1.0-mm). Criteria for interrupting the exercise test were ST-segment depression ≥3.0 mm, ST-segment elevation ≥2.0 mm, maximum age-related heart rate, severe chest pain, physical exhaustion, severe arterial hypotension, severe arterial hypertension, and complex or sustained arrhythmias or both. The following parameters were systematically measured: resting heart rate and arterial blood pressure, heart rate and arterial blood pressure at peak exercise, T1.0-mm in seconds, rate pressure product

Table 1—*Main demographic, biochemical, and clinical characteristics of the study population*

	R group	V group	*P*
N	42	54	
Male sex	37 (88)	49 (91)	0.744
Age (years)	61 ± 9	63 ± 7	0.224
Smoking	9 (24)	5 (12)	0.094
Plasma glucose (mg/dL)	155 ± 42	144 ± 60	0.315
HbA_{1c} (%)	7.3 ± 1.9	7.2 ± 1.8	0.793
Total cholesterol (mg/dL)	161 ± 41	153 ± 37	0.319
HDL cholesterol (mg/dL)	41 ± 14	38 ± 10	0.224
LDL cholesterol (mg/dL)	96 ± 34	89 ± 29	0.279
Tryglicerides (mg/dL)	134 ± 63	146 ± 84	0.442
Prior myocardial infarction	17 (45)	23 (56)	0.842
High blood pressure	15 (36)	20 (48)	0.888
Two-vessel disease	14 (33)	19 (35)	0.842
Three-vessel disease	28 (67)	35 (65)	0.842
Ejection fraction (%)	64 ± 7	62 ± 4	0.081

Data are means ± SD or *n* (%) unless otherwise indicated. Vessel disease: coronary vessel obstruction by coronary angiography. NS, not significant.

(RPP) at the onset of ST-segment depression, and exercise duration in seconds.

IPC analysis

The improvement in ischemic parameters in ET1 compared with ET2 indicates the presence of IPC. The following parameters were assessed to evaluate IPC: T1.0-mm and RPP.

Statistical analysis

Two-factor ANOVA with repeated measures was used to compare RPP and T1.0-mm data for groups R and V. Comparisons of the remaining continuous or discrete variables between the two groups were performed using an unpaired Student t or a χ^2 test, respectively. Fisher test was used when appropriate. Data were expressed as means ± SD. A value of $P < 0.05$ was considered significant. Results are expressed as means ± SD.

RESULTS—The main demographic, biochemical, and clinical characteristics of the ninety-six patients are presented in Table 1. Both groups R ($n = 42$) and V ($n = 54$) had homogeneous characteristics (P = not significant).

Results of treadmill exercise tests

All 96 patients in R and V groups achieved 1.0-mm ST-segment depression during the exercise tests (ET1, -2, -3, and -4).

Phase 1 (without drugs)

During phase 1, all patients (42 in group R and 54 in group V) demonstrated improvement in the T1.0-mm and RPP in ET2 compared with ET1, demonstrating IPC (Tables 2 and 3).

Phase 2 (with drugs)

Group R. After R for 7 days, 35 patients (83%) experienced ischemia earlier in ET4 than in ET3 (299 ± 92 vs. 337 ± 121, respectively, $P = 0.0001$). The RPP in ET4 and ET3 (25,898 ± 5,739 vs. 25,292 ± 4,419) showed no statistical significance. These results indicated cessation of IPC. Only seven patients (17%) demonstrated greater T1.0-mm in ET4 than in ET3 (271 ± 139 vs. 247 ± 105, P = NS), as was the case with RPP (22,087 ± 2,438 vs. 19,768 ± 3,108, P = not significant) (Table 2).

Group V. After V for 7 days, 41 patients (76%) had preserved IPC, as observed in T1.0-mm and RPP results. T1.0-mm and RPP were significantly greater during ET4 compared with ET3 (T1.0-mm 389 ± 114 vs. 325 ± 116, respectively, $P < 0.001$, and RPP 25,574 ± 6,256 vs. 22,733 ± 4,612, $P < 0.001$). Only 13 patients (24%) had IPC abolished. T1.0-mm and RPP were lower in ET4 than in ET3 (272 ± 133 vs. 307 ± 135 and 22,245 ± 3,780 vs. 23,232 ± 4,380, respectively) (Table 3).

R preserved IPC in 7 (17%) of 42 patients, while V preserved in 41 (76%) of 54 patients ($P < 0.0001$). The number and percentage of patients with IPC abolished and preserved in the R and V groups are demonstrated in Fig. 1.

CONCLUSIONS—The increased tolerance to myocardial ischemia observed during the second of two sequential exercise tests, e.g., the warm-up phenomenon, has been proposed as an effective clinical model of IPC (3–8). In this model, the comparison of T1.0-mm between sequential treadmill exercise tests is a reliable index to demonstrate the warm-up phenomenon (24).

In the same way, it is well established that RPP at 1.0-mm ST-segment depression represents a noninvasive index of myocardial O_2 consumption at the ischemic threshold, which can be improved by preconditioning (3,5,6,25).

The mechanism of the warm-up phenomenon is not totally understood. Rizi et al. (26) and Ylitalo et al. (27) have previously suggested that the warm-up phenomenon could be related to an increase in coronary flow. On the other hand, Williams et al. (28) and Okazaki et al. (3) have demonstrated in patients with CAD that the warm-up phenomenon is relative to a reduction in myocardial O_2 consumption rather than an increase in coronary blood flow. Accumulation of evidence has suggested that K_{ATP} channels play a relevant role in myocardial cytoprotection (29,30). It has been postulated that the opening of the channel is responsible for the shortening of action potential duration observed during ischemia. The consequent reduction in Ca^{2+} influx may lead to reduced myocardial contractility and vasodilatation, thus saving ATP. In this way, K_{ATP} channel–opening drugs, e.g., nicorandil, cromakalin, and pinacidil, were able to mimic the effect of IPC protection (12). In contrast, glibenclamide, which is a nonselective K_{ATP} channel blocker, has been consistently related to loss of preconditioning response during sequential treadmill exercise testing (12–14).

The major aim of this study was to assess the effects of R and V on myocardium during exercise-induced ischemia in terms of evaluating their effect on IPC in patients with type 2 diabetes and stable CAD. Both indexes, tolerance to myocardial ischemia and ischemic threshold, were analyzed in our study for evaluation of IPC. In the presence of R, our results showed loss of improvement in tolerance to myocardial ischemia and to myocardial O_2 at the ischemic threshold and, therefore, the loss of IPC. R differs structurally from the sulphonylureas, but it interacts with a site common to all types of SURs. This leads to the inhibition of cardiac muscle and β-cell K_{ATP} channel activity (18). In this same scenario, after glibenclamide administration, Ovünç (13) found T1.0-mm and RRP in two exercise tests. Furthermore, Ferreira et al. (14) showed that chronic use of glibenclamide

Table 2—*T1.0-mm and RPP of the R group with abolished and preserved IPC*

IPC	ET1	ET2	*P**	ET3	ET4	*P***
Abolished ($n = 35$)						
T1.0-mm	330 ± 114	337 ± 120	0.0001	337 ± 121	299 ± 92	0.0001
RPP	27,430 ± 4,798	27,739 ± 4,537	0.008	25,292 ± 4,419	25,898 ± 5,739	NS
Preserved ($n = 7$)						
T1.0-mm	230 ± 74	317 ± 102	0.0040	247 ± 105	271 ± 139	NS
RPP	25,633 ± 4,359	26,471 ± 5,437	NS	23,089 ± 4,126	23,966 ± 2,675	NS

Data are means ± SD. RPP was measured as follows: bpm × mmHg. *ET1 versus ET2. **ET3 versus ET4.

Table 3—*T1.0-mm and RPP of the V group with abolished and preserved IPC*

	ET1	ET2	*P**	ET3	ET4	*P***
IPC abolished (*n* = 13)						
T1.0-mm	291 ± 123	349 ± 126	<0.001	307 ± 135	272 ± 133	0.006
RPP	23,414 ± 5,011	26,250 ± 4,478	0.004	23,232 ± 4,380	22,245 ± 3,780	0.144
IPC preserved (*n* = 41)						
T1.0-mm	271 ± 100	356 ± 109	<0.001	325 ± 116	389 ± 114	<0.001
RPP	22,174 ± 4,291	25,403 ± 4,874	<0.001	22,733 ± 4,612	25,574 ± 6,256	<0.001

Data are means ± SD. RPP was measured as follows: bpm × mmHg. *ET1 versus ET2. **ET3 versus ET4.

eliminated the improvement in ischemic threshold during the second exercise test but did not interfere with the tolerance to exercise (14). In fact, the demonstration of the loss of IPC by hypoglycemic drugs in patients with type 2 diabetes and CAD may suggest worse outcomes during acute ischemia. Thus, according to results of our study, it is reasonable to say that R abolished IPC by mechanisms similar to those associated with glibenclamide.

On the other hand, the opposite effect was found when we analyzed the results of V, which maintained myocardial preconditioning in the second of two exercise tests, resulting in improvements in tolerance to myocardial ischemia and to myocardial O_2 consumption at the ischemic threshold in two sequential treadmill exercise tests.

V acts in heart mainly by binding of GLP-1 in GLP-1R (22,31). A number of G-protein–coupled receptors have been shown to be involved as triggers of IPC and include adenosine A1 and opioid d1 receptors. It is thought that these receptors activate a G-protein (Gi or Gq) that leads to activation of protein kinase C and other intracellular kinases, such as tyrosine kinases or the mitogen-activated protein kinase pathway. Such receptors have been reported to mediate cardioprotection, and they seem to be the potential therapeutic target for clinical use (32). Multiple preclinical studies have demonstrated cardioprotective effects of GLP-1R agonists in experimental models of ischemic heart disease. Studies have shown that the cardioprotective effect of GLP-1 analogs limits myocardial infarct size in various animal models (33–35). In this setting, GLP-1 infusion improved regional and global left ventricular function in patients with acute myocardial infarction and severe systolic dysfunction after successful primary angioplasty (36). However, these results depend on a GLP-1R agonist at a high concentration or through supraphysiological GLP-1 signaling. In fact, there are few trials about cardioprotective effects of oral DPP-4 inhibitors. Although GLP-1 is viewed as an important DPP-4 substrate able to influence cardiovascular function, DPP-4 cleaves multiple peptides, which may have direct actions on the heart and blood vessels (20). Preclinical studies have demonstrated cardioprotection after genetic or pharmacological reduction of DPP-4 activity (37,38). Read et al. (39) demonstrated that acute administration of the DPP-4 inhibitor improved myocardial response to dobutamine stress echocardiography and reduced features of myocardial stunning in patients with ischemic heart disease. Our results show that V preserved the warm-up phenomenon in patients with type 2 diabetes and CAD. The cardioprotective effect was demonstrated by the increased tolerance to myocardial ischemia and ischemic threshold index during the second of two sequential exercise treadmill tests.

Even though the results showed different responses between the groups after the use of hypoglycemic agents, this finding supports the effect of the different drugs in similar populations. The isolated analysis of phase 1 showed a physiological and functional similarity in these groups.

Although both groups presented the same degree of cardiac impairment and same ischemic response with no relevant differences, there were 7 of 42 patients with IPC preserved after R and 13 of 54 patients with abolished IPC after V. These differences observed in R and V groups reveal the degree of complexity of IPC mechanisms in the presence of ischemic insult. Moreover, although some parameters of exercise-induced ischemia have been reached to demonstrate the IPC expression, there are no established limits.

Our findings demonstrate that IPC, as a complex and dynamic phenomenon, can be the target of drug activities affecting the ability of the heart to adapt to ischemic stress. The analysis of two different roles of IPC suggests that they probably activated different survival pathways in the myocardium. It supports the importance of identifying underlying mechanisms of endogenous myocardial protection to improve the protective effect of pharmacological therapy. In summary, this study revealed that V had a better effect on the myocardium and, hence, maintained IPC protection under conditions of stress-induced ischemia. On the other hand, R prevented the IPC protection under the same clinical conditions. These data may eventually be

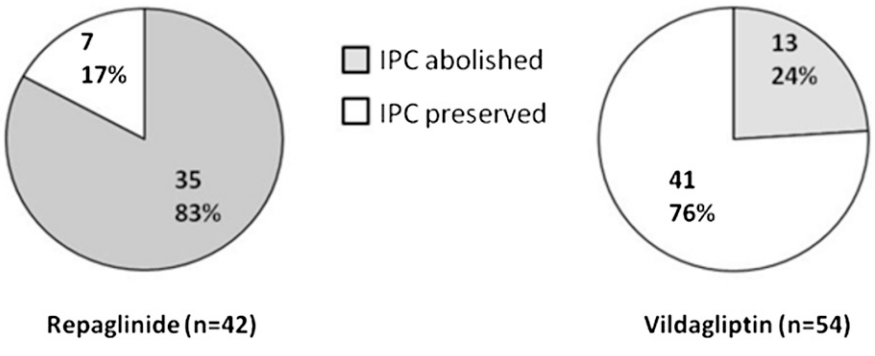

Figure 1—*Pie charts showing the number and percentage of patients with IPC abolished and preserved in the R and V groups.*

important in allowing us to reflect on the optimal therapy for patients with type 2 diabetes and CAD. Certainly, further investigation is important to realize the full clinical potential of IPC. For the past 25 years, the scientific community has accomplished many trials to understand the IPC mechanisms in order to correlate their effects on the morbidity and mortality associated with myocardial infarction. Schramm et al. (40), in an epidemiological study discussing mortality in patients receiving different oral hypoglycemic agents, showed different degrees of effect on IPC. However, the precise relationships and mechanisms underlying these effects await further large studies.

Clinical considerations

The delicate and complex balance of ischemic myocardium at rest and the protective mechanisms achieved during the stress-induced coronary ischemia may be influenced by oral hypoglycemic agents and increase the risk of cardiovascular events. Furthermore, the therapeutic options for diabetes treatment go beyond glucose-lowering efficacy in populations with increased risk of coronary ischemic events. Indeed, for a greater understanding of the risks and benefits of these drugs, we need more clinical trials with larger sample sizes and longer follow-up to evaluate the incidence of major cardiovascular events in this select group of patients.

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R.M.R. researched data and wrote the manuscript. A.H.U. and P.C.R. contributed to exercise treadmill tests and data analysis. E.G.L. and C.L.G. reviewed the manuscript. D.F. reviewed the manuscript and contributed to statistical analysis. C.M.C.S., M.T., and P.G. researched data. W.H. conceived this study, contributed to discussion, and reviewed the manuscript. R.K.F. and J.A.F.R. reviewed the manuscript. W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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