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Microvascular ischemia in patients with successful percutaneous coronary intervention: effects of ranolazine and isosorbide-5-mononitrate

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Abstract. – OBJECTIVE: About one-third of patients undergoing percutaneous coronary interventions (PCIs) for flow-limiting coronary stenosis continue to develop signs of myocardial ischemia (MI) during exercise stress test [EST], despite successful coronary revascularization. Coronary microvascular dysfunction is a likely major cause of the persistence of EST-induced MI in these patients.

PATIENTS AND METHODS: We studied 15 patients (14 men, age 67±5 years) fulfilling the following strict inclusion criteria: (1) recent PCI (<6 months), with drug-eluting stent, of coronary artery stenoses for stable angina, with evidence of full success (no residual stenosis >20% in any vessel); (2) persistence of ST-segment depression induction during EST.

After a basal investigation, patients received either ranolazine (375 mg bid) or isosorbide-5-mononitrate (ISMN, 20 mg bid) for 3 weeks in a single-blind, randomized crossover study. Clinical assessment, symptom-limited EST, echocardiographic color-Doppler, with tissue-Doppler examination, and coronary microvascular dilator response to adenosine (CFR-ADO) and cold pressor test (CFR-CPT), assessed by transthoracic echo-Doppler, were obtained at baseline and the end of the 3-week therapy with each drug.

RESULTS: Compared to both baseline and ISMN, ranolazine showed a longer time to 1 mm ST-segment depression (404±116 s *vs.* 317±98 and 322±70 s, respectively; $p<0.01$). No differences were observed in coronary microvascular function and diastolic left ventricular function between the 2 drugs and compared to baseline.

CONCLUSIONS: Our data show that ranolazine, but not ISMN, improved time to ischemia during EST. This effect, however, was independent of any effects on coronary microvascular and diastolic function.

Key Words:
Microvascular circulation, Percutaneous coronary intervention, Ranolazine, Nitrates.

Introduction

About one-third of patients undergoing percutaneous coronary interventions (PCIs) of flow-limiting coronary artery stenosis continue to report episodes of angina and/or develop signs of myocardial ischemia during exercise stress test (EST), despite the angiographic evidence of successful complete coronary revascularization[1-4].

In these patients, coronary microvascular dysfunction (CMVD) is a major cause of persistent EST-induced myocardial ischemia[5-7], and a more severe impairment of coronary microvascular dilatation has been shown to predict restenosis[8]. Yet, whether CMVD and signs and symptoms of myocardial ischemia can be improved in these patients is unknown. The effects of traditional anti-ischemic medications are poorly known, although some benefits have been reported with amlodipine in a trial[9].

We and others have recently shown significant beneficial effects in patients with MVA with ranolazine[10-13]. Ranolazine is a novel anti-ischemic drug that seems to mainly act by improving left ventricular diastolic function through inhibition of the late sodium current, which prevents intracellular calcium overload during ischemia[14-16].

In this study, we aimed to assess whether ranolazine may improve EST results in patients with persistent positive EST after successful PCI. The effects of ranolazine were compared with those of isosorbide-5-mononitrate (ISMN),

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a nitrate that, according to previous data[17-21], was expected to have limited effects on CMVD of these patients.

Patients and Methods

Patients

We enrolled 15 consecutive patients who fulfilled the following inclusion criteria: (1) previous percutaneous transluminal coronary angioplasty (PTCA) with stenting; (2) exercise-induced ST-segment depression ≥1 mm, with or without a history of typical effort angina; (3) no obstructive coronary artery disease at a recent (<6 months) coronary angiography; (4) no significant systemic disease (e.g., liver and/or kidney failure, tumors, neuromuscular disorders, psychiatric diseases); (5) no ECG abnormalities that could interfere with the assessment of ST-segment during exercise; (6) no previous consumption of the drugs under investigation and no contraindications to their administration.

Study Design

Patients were enrolled in an open crossover study in which, in addition to their current therapy, they received, in a random order and for 3 weeks each, either ISMN (20 mg twice a day in a slow-release formulation) or ranolazine (375 mg twice a day).

A washout period of 1 week separated the 2 phases of the study. After 1 week of each treatment, patients underwent a clinical visit and a 12-lead electrocardiogram (ECG) to assess tolerability of therapy and exclude side effects. In patients who reported significant side effects potentially related to the drugs, the dosage was reduced to 20 mg once a day for ISMN and to 375 mg once a day for ranolazine.

The following clinical and diagnostic tests were performed at enrollment and at the end of each of the 2 periods of treatment: (1) maximal symptom/sign-limited exercise stress test (EST); (2) echocardiographic color-Doppler, with tissue-Doppler, examination, (3) assessment of coronary microvascular dilator response to adenosine (ADO) and cold pressor test (CPT) by transthoracic echo-color-Doppler.

The study complies with the Declaration of Helsinki and was approved by the local Ethics Committee of our Institution. All patients were informed of the purpose and nature of the study and provided written, informed consent for participation.

Exercise Stress Test

EST was performed following a standard Bruce protocol. Three ECG leads (DII, V2, and V5) were continuously monitored during the test, and up-to-date averaged QRS complexes of all ECG leads were continuously displayed on the screen. An ECG was printed and blood pressure was measured at baseline, at the end of each stage, at peak EST, when clinically indicated and at 1-minute intervals in the recovery phase. EST was stopped in cases of physical exhaustion, progressive angina (Borg scale >6), ST-segment depression >4 mm, or relevant clinical events (e.g., dyspnea, hypotension, arrhythmias, hypotension).

ST-segment depression was considered significant if it was horizontal or downsloping and ≥1 mm at 0.08 seconds from the J-point in at least 3 consecutive beats in any lead. If EST was negative, in statistical analyses time, heart rate and blood pressure at 1 mm ST-segment depression and at angina were considered those recorded at peak EST.

Echocardiography

Mono-bidimensional color- and tissue-Doppler echocardiography was performed using the ultrasound equipment Artida Toshiba (Toshiba Italy, Rome, Italy), using a 3.5-MHz probe to assess diastolic function.

Patients were positioned in the left lateral decubitus position and 4-chamber apical view was obtained. The sample volume of the pulsed-wave Doppler was positioned immediately below the central point of contact of the two mitral leaflets in systole and the Doppler profile of the mitral flow was recorded. The E wave and A wave peaks were measured and the E/A wave ratio was calculated as an index of diastolic function. An impaired diastolic function was diagnosed in case of E/A ratio <0.75.

Left ventricular diastolic function was also assessed by tissue-Doppler imaging, measuring the speed of displacement of the mitral annulus at the level of the lateral and septal wall. The echographic signal obtained at this level shows three different components: a peak systolic wave (S_m) and two waves of opposite polarity (E_m and A_m) during the early and late phase of diastole, respectively. From pulsed-wave Doppler and tissue-Doppler images, we obtained the E/E_m ratio. This ratio, indeed, has been demonstrated to correlate better than the E/A ratio with left ventricular filling pressure and, therefore, to better assess left ventricular diastolic function.

Table I. Main clinical and angiographic characteristics of study population.

Age (years)	67.3 ± 5.4
Males/females	14/1
Body mass index (kg/m2)	26.3 ± 2.9
Left ventricular ejection fraction (%)	61.4 ± 3.0
Cardiovascular risk factors	
Family history of CVD	8 (53%)
Hypertension*	12 (80%)
Hypercholesterolemia†	15 (100%)
Diabetes mellitus	7 (47%)
Drug therapy	
β-Blockers	13 (87%)
Calcium antagonists	2 (13%)
Antiaggregants	15 (100%)
ACE-inhibitors/ARBs	12 (80%)
Diuretics	1 (6%)
Statins	15 (100 %)
Oral antidiabetic drugs	5 (33%)
Insulin	1 (6 %)
Percutaneous coronary intervention	
Left anterior descending artery	13 (87%)
Left circumflex artery	4 (27%)
Right coronary artery	9 (60%)

ACE = angiotensin-converting enzyme; ARBs = angiotensin-II receptor blockers; CVD = cardiovascular disease. *Blood pressure ≥140/90 mm Hg or consumption of any antihypertensive drug. †Total blood cholesterol >200 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, or consumption of lipid-lowering drugs.

Coronary Microvascular Function

Coronary microcirculation dilator function was assessed noninvasively by measuring the increase in coronary blood flow (CBF) in response to an endothelium-independent stimulus (adenosine) and to an endothelium-dependent stimulus (cold pressor test, CPT), using transthoracic Doppler echocardiography.

Briefly, in each patient, the left anterior descending coronary artery or the left circumflex artery was imaged with a 3.5 MHz transducer connected to the same ultrasound equipment used for the previous test. Diastolic CBF velocity was recorded by pulsed-wave Doppler signal both at rest and at the peak of 90-sec intravenous infusion of adenosine (140 μg/kg/min), under ECG and blood pressure monitoring.

After 15 minutes from heart rate and blood pressure recovery to basal values of, basal CBF velocity was recorded again. Then, CPT was performed by putting the patient's left hand in ice water for 90 seconds, and CBF was measured at the end of the test.

For each of the two tests (adenosine and CPT), CBF velocity at baseline and at the peak of the test was obtained as the average of three measurements made during diastole of three consecutive cardiac cycles. The coronary vasodilator response was calculated as the ratio between CBF velocity at the peak of adenosine/CPT test and the respective basal value.

Statistical Analysis

Continuous and discrete variables were reported as means (with standard deviation) and proportions, respectively. Global comparisons among basal, ranolazine and ISMN data were done by repeated measure analysis of variance (ANOVA) and chi-square test for continuous and categorical variables, respectively. In case of statistical significance, multiple between-group comparisons were done by paired **t**-test and chi-square test with Bonferroni correction. Statistical analysis was performed with SPSS 21.0 software. A $p < 0.05$ was always required for statistical significance.

Results

The main clinical and angiographic data of patients are shown in Table I, whereas Table II summarizes the EST results. At baseline, all patients developed significant ST-segment depression during EST, whereas angina was reported by 2 patients only. Both ranolazine and ISMN did not cause any significant effects on most of the exercise parameters. However, compared to both baseline and ISMN, time to 1 mm ST-segment depression was significantly prolonged by ranolazine (p=0.01).

Both ranolazine and ISMN had no significant effects on CBF response to both adenosine and CPT, as well as on left ventricular diastolic function (Table III).

Discussion

A sizeable number of patients who undergo successful coronary artery stent implantation continues to show signs of myocardial ischemia at EST and, in some cases, also complain of chest pain[1-4], despite optimal classical anti-ischemic therapy.

Although the mechanisms of persistent ischemia may be multiple, a pivotal role of CMVD has been suggested by several studies[5-7]. Of note, we recently demonstrated that CMVD is associated

Table II. Main results of exercise stress test.

	Baseline	Ranolazine	ISMN	p
Baseline				
Systolic BP (mmHg)	126 ± 10	123 ± 15	127 ± 10	0.25
Diastolic BP (mmHg)	73 ± 7	73 ± 10	74 ± 9	0.93
Heart rate (bpm)	68 ± 9	67 ± 9	67 ± 8	0.75
RPP (bpm*mmHg)	8577 ± 1065	8143 ± 1378	8451 ± 1451	0.37
1-mm ST depression				
Systolic BP (mmHg)	153 ± 17	151 ± 14	147 ± 14	0.36
Diastolic BP (mmHg)	77 ± 12	76 ± 15	72 ± 11	0.39
Heart rate (bpm)	120 ± 17	118 ± 15	116 ± 13	0.56
RPP (bpm*mmHg)	18441 ± 3972	17757 ± 2315	17037 ± 3016	0.32
Time (s)	317 ± 98	404 ± 116*	322 ± 70	0.001
Maximal STD (mm)	1.8 ± 0.6	1.6 ± 1.1	1.9 ± 1.1	0.24
Peak exercise				
Systolic BP (mmHg)	169 ± 15	168 ± 14	163 ± 12	0.43
Diastolic BP (mmHg)	83 ± 12	79 ± 12	76 ± 12	0.11
Heart rate (bpm)	141 ± 17	138 ± 18	139 ± 15	0.69
RPP (bpm*mmHg)	23930 ± 3683	23225 ± 3546	22749 ± 3157	0.39
Time (s)	550 ± 110	584 ± 95	581 ± 117	0.06
1-minute recovery				
Heart rate (bpm)	122 ± 13	120 ± 13	118 ± 13	0.26

BP = blood pressure; RPP = rate pressure product. *p<0.01 vs. both baseline and ISMN.

with persistent positivity of EST after successful PCI[7] and, importantly, it may predict coronary restenosis during follow-up[8].

In a previous study, we showed that ranolazine was helpful for improving symptoms and EST results in patients with primary stable microvascular ischemia/angina[10], in agreement with the results of other studies[11-13]. The improvement, however, did not seem to be associated with improvement of coronary microvascular function.

In this study, ranolazine increased time to myocardial ischemia during EST in patients with CMVD associated with previous obstructive CAD. In agreement with our previous data, however, ranolazine did not improve CMVD, suggesting that other mechanisms are involved in this favorable effect. Of note, ranolazine also did not significantly improve left ventricular diastolic function and had also no effect on myocardial oxygen consumption (as expressed by the rate-pressure product) at ischemic threshold. Thus, some effects on delaying the achievement of the ischemic threshold seem to play a major role in its effect on time to myocardial ischemia[22,23]. Although the exact mechanism cannot be derived from our data, we are tempting to speculate that an improvement of the energetic metabolism of the myocardium by ranolazine[24,25] might improve myocardial efficiency during EST, thus delaying the achievement of ischemic threshold.

The lack of effect of ISMN on microvascular function in our patients furtherly shows the li-

Table III. Coronary microvascular function and left ventricle diastolic function.

	Baseline	Ranolazine	ISMN	p
CFR-ADO	1.33 ± 0.16	1.39 ± 0.29	1.36 ± 0.21	0.42
CFR-CPT	1.15 ± 0.09	1.18 ± 0.15	1.17 ± 0.13	0.75
E/A wave ratio (s)	0.86 ± 0.23	0.80 ± 0.16	0.87 ± 0.30	0.45
E/E' wave ratio (s)	7.37 ± 2.19	6.75 ± 2.02	6.35 ± 1.79	0.12

CFR-ADO = coronary flow response to adenosine; CFR-CPT = coronary flow response to cold pressor test.

mited usefulness of long-acting nitrates in ischemic conditions caused by CMVD. The development of tolerance, however, might have also contributed to the absence of benefits found in our study[14-21].

Finally, only two our patients among those enrolled reported persistence of angina symptoms after PCI, thus not allowing a reliable assessment of the drugs on the symptomatic state of patients. It is worth noting, however, that in both patients ranolazine (but not the ISMN) was found to improve symptoms, along with signs of ischemia.

Conclusions

In summary, our data show that ranolazine, but not ISMN, improves time to ischemia during EST in patients with successful PCI but persistent exercise-induced ST-segment depression. This effect was not associated with any significant changes in coronary microvascular and diastolic function.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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