Effects of Ivabradine on residual myocardial ischemia after PCI evaluated by stress echocardiography.

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INTRODUCTION

Stable angina is a syndrome characterized by a transitory condition of acute myocardial ischemic attacks caused by an imbalance between myocardial perfusion and metabolic demand [1]. The antianginal drugs and the percutaneous coronary revascularization, are essential to treat the persistent symptoms. However, in some cases, when small vessels or side branches are significantly involved with hard or impossible reperfusion, drug therapy is the only strategy to prevent the worsening of ischemic heart disease and to reduce the symptoms. Heart rate is the major determinant of cardiac output and myocardial oxygen consumption, therefore the reduction of heart rate in patients with stable angina can be considered a goal of the therapy [2]. Ivabradine is an antianginal agent that specifically inhibits the pacemaker (If) current, resulting in selective HR reduction with no negative effects on blood pressure and inotropism [3]. In patients with chronic heart failure, Ivabradine improves clinical outcomes if used with beta-blockers under well documented efficacy and safety [4].

In previous studies, Ivabradine reduced anginal symptomatology but has not clearly demonstrated improvements of the outcomes in patients with chronic ischemic disease without left-ventricular systolic dysfunction [5-7]. More recently, in CONTROL-2 Study, in patients with stable angina, the combination of the two therapies ivabradine and β-blockers together demonstrated good tolerability, safety, and also pronounced clinical improvements, compared to β-blockers up titration [8]. Moreover, an interesting SHIFT substudy showed the reversed LV remodeling with marked reductions of LV volumes and significant improvements of LV ejection fraction (LVEF) in patients treated with Ivabradine [9].

In this context, in order to define the role of Ivabradine in patients with residual angina after PCI, we aimed to quantify the clinical benefits of adding ivabradine to standard antischemic therapy, in symptomatic patients for residual myocardial ischemia after PCI, using more precise indicators of oxygen consumption.

Furthermore, we studied the effects of ivabradine on diastolic function (both at rest and after exercise) and on the ventricular remodeling.

METHODS.

We investigated the efficacy of treatments with Ivabradine in addition to full anti-ischemic therapy (as per guidelines) compared with the latter alone in patients with signs or symptoms of residual angina underwent percutaneous coronary intervention plus stent implantation. The main purpose was to evaluate if addition of ivabradine to standard therapy might increase the threshold for angina improving the stress tolerance and exercise duration in terms of double product (DP) and triple product (TP), respectively calculated as a product between HR and systolic blood pressure and the product between DP and ejection time. In our opinion these, indirectly, reflect the true myocardial oxygen consumption (MVO2) and the improvement of mechanical load that the ventricle can withstand at different levels of exercise. Triple product is closely related to the tension-time index, a measure of ventricular work and oxygen demand that is found by multiplying the average pressure in the ventricle during the period in which it ejects blood by the time it takes to do this [10].

The second objective was to evaluate changes at rest and after the stress test of diastolic function and ventricular remodeling, using echocardiographic parameters.

Study Population

In this randomized, prospective, single-center study, all the patients selected were with chronic coronary artery disease undergoing percutaneous coronary intervention (PCI) plus stent implantation, residual angina and on treatment with full anti-ischemic therapy with and without Ivabradine. In all patients, revascularization was complete as far as possible, all coronary lesions resulting in a stenosis greater than 50% in vessels of a caliber greater than two millimeters were treated. The inclusion criteria was: coronary artery disease with chronic stable angina for more than three months (Canadian Cardiovascular Society–CCS-class I-III); percutaneous revascularization with stent implantation at least one; signs/symptoms of residual ischemia; sinus rhythm; HR ≥ 70 bpm at rest; ability to perform an echocardiogram stress test with the tilting bicycle stress test (BST); good acoustic window; age ≥ 18 years. The main exclusion criteria were: drugs intolerance or hypersensitivity, EF ≤ 40 % with NYHA class III to IV; CCS IV; atrial fibrillation or flutter; presence of a pacemaker or implantable defibrillator; II or III degree AV block; HR ≤ 70 bpm at rest or sick sinus syndrome; any condition that could interfere with the ability to exercise stress test like Wolff- Parkinson-White syndrome, left bundle branch block, left ventricular hypertrophy; rate-corrected QT interval (QTc) greater than 500 ms or the use of drugs that prolong the QTc interval; symptomatic hypotension or uncontrolled hypertension (systolic blood pressure at rest ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg); severe liver disease and severe renal impairment (creatinine clearance ≤ 30 ml/min); electrolyte disorders; uncontrolled thyroid disease and pregnancy. All patients signed informed consent prior to randomization. The study was designed according to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee and Institutional Review.

Study design and Treatment

All patients with CCS I-III angina, were considered and only patients who met the inclusion criteria, after signing the informed consent form, were included in our study. The treatment was assigned on the basis of a 1:1 ratio to receive Ivabradine 5 mg twice daily (Ivabradine Group, IG) or standard therapy according to the guidelines (Control Group, CG). Both therapeutic strategies were titrated to the maximum tolerated dose, in particular β-blockers. All patients were submitted to clinical evaluation and exercise stress echocardiography at enrollment time (T1) and after 30 days of therapy (T2). During the period between exercise stress tests, clinical evaluation with ivabradine therapy up-titration was performed after 15 days.

Patient evaluation included physical examination, HR measurement by 12-lead electrocardiograms (ECG), two-dimensional, Doppler and Tissue Doppler echocardiography, using Philips iE33 system (Andover, Massachusetts, USA) and a supine bicycle ergometer stress test. During the test, operators recorded echocardiograms before and during the exercise. The parameters measured were: left ventricular (LV) 2D diameters, systolic function parameters, ejection time, LV end-systolic and end-diastolic volumes in relation to body surface area (end-diastolic and end-systolic indices [EDI and ESI]), and LV ejection fraction (LVEF) were assessed according to Simpson's method (as suggested by the American Society of Echocardiography and European Association of Echocardiography) [11].

Bicycle Stress Test. Exercise test, was performed using a semi-recumbent and tilting bicycle ergometer (X-SCRIBE EKG Analysis, Mortara Instruments; Ergometrics 800s, Ergoline West-Germany) with an initial workload set at 25 Watt and increments of 25Watt/ 2 min. HR and rhythm is continuously recorded using a 12-lead electrocardiogram, blood pressure was measured at baseline, at peak exercise, and during the last minute of each stage including recovery.

The rate of exercise, which was measured in metabolic equivalents (1 metabolic equivalent = 3.6 ml/kg/min), and the duration of exercise were assessed as well.

Chronotropic reserve was estimated using the formula: 100 × (peak HR–resting HR) / (220–age) – resting HR.

Stress test was interrupted if the patient developed chest pain, ST segment elevation > 0.1 mV at 80 ms from the J point, or a significant adverse event (significant ventricular arrhythmia, limiting breathlessness, dizziness, muscular exhaustion, chest pain, arterial pressure drop ≥ 10 mmHg with symptoms, or severe systemic hypertension).

Echocardiography. Images were acquired in standard views and displayed side by side in a quad-screen format. All images were digitally recorded in continuous-loop format. Total work at the ischemic threshold and peak exercise were calculated. Double product (DP) was calculated during the last stage of exercise performed by multiplying maximum systolic BP by maximum HR; triple product (TP), was obtained integrating DP with ejection time (ET) measured with mitral annular PW-TDI (BP x SBP x ET).

In addition diastolic function was evaluated by PW Doppler E and A waves, TDI derived E' measurements and E/E' ratio. Mitral annular E' velocity was estimated as the average between lateral and septal velocity.

Drugs with possible interactions with ivabradine such as non-dihydropyridine calcium channel blockers, class I antiarrhythmics and strong inhibitors of cytochrome P450 3A4, were not allowed, whereas short-acting nitrates were allowed up to 3 hours before exercise or after exercise if needed.

At the end of the tests, double, triple products and diastolic function evaluation, were collected by a blind operator.

All parameters recorded and calculated in off-line analysis were included in our register.

Statistical analysis.

The sample size was not calculated because it was a pilot study. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentages. Categorical variables were compared among groups using the chi-square test or Fisher's exact test when appropriate, whereas continuous variables were compared with Student t-test. All tests were two-sided and a p value less than 0.05 was considered statistically significant. All analyses were performed using SPSS software, version 20.0 for Windows.

COMPLIANCE WITH ETHICAL STANDARDS

All authors declare that they have no conflict of interests. No funding was received for this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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