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Heart rate control with oral ivabradine in computed tomography coronary angiography: A randomized comparison of 7.5 mg vs 5 mg regimen ☆

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ABSTRACT

Background: Heart rate (HR) reduction is essential to achieve optimal image quality and diagnostic accuracy with computed tomography coronary angiography (CTCA). Administration of oral ivabradine seems to be more effective than beta-blockade in reducing HR in patients referred for CTCA.

Methods: Two-hundred-fifty-nine consecutive patients referred for CTCA were prospectively enrolled. Patients not receiving beta-blocker at baseline (group 1) and those with beta-blocker therapy (group 2) were enrolled in the study. Each group was randomized into 3 parallel arms with 1:1:1 allocation. Patients who did not receive beta-blocker at baseline: underwent CTCA without beta blocker (n = 49), and received ivabradine 5 mg (n = 48), or 7.5 mg ivabradine (n = 48). Patients with beta-blocker therapy: continued with the prior beta-blocker without any dose modification (n = 38), and received ivabradine 5 mg (n = 38), or ivabradine 7.5 mg (n = 38).

Results: HR and blood pressure were assessed at admission (T0), immediately before CTCA (T1) and during CTCA (T2). Administration of ivabradine 7.5 mg significantly reduced mean relative HR at T1 and T2 ($p<0.01$), the rate of patients not achieving target HR at T1 ($p<0.001$) and T2 ($p<0.01$), and the percentage of patients needing additional IV beta-blockade prior to CTCA ($p<0.01$). Results remained statistically significant even after correction for age, gender, ejection fraction, risk factors and HR at T0, in a multivariable analysis.

Conclusions: Ivabradine 7.5 mg is more effective than ivabradine 5 mg in increasing the rate of patients at target HR in patients referred for CTCA.

1. Introduction

Computed tomography coronary angiography (CTCA) represents a useful tool for the diagnosis of coronary artery disease (CAD) and its related prognostic significance [1–3]. As the field of CTCA continues to advance, its ability to analyze stenosis severity as well as plaque burden and composition is more accurate [4–8]. A very high negative predictive value, ranging from 93% to 100%, in ruling-out significant coronary stenosis is shown [9–11]. The procedure leads to radiation exposure and contrast medium injury. An international multicenter observational study showed that a 5% increase in radiation exposure was due to an increase of 10 bpm [12]. The reduction of radiation exposure has been achieved by the technological improvement, even though almost all the algorithms are more effective at lower heart rate (HR).

In order to achieve the ambitious results that CTCA aspires, an adequate image quality is mandatory since the diagnostic accuracy is strictly correlated. In this respect, a low and stable HR is an important prerequisite. It is well known that the increase in HR is associated with an almost linear deterioration of image quality [13–15]. Accordingly, to minimize coronary artery motion artifacts, specific values of HR have to be reached depending on the different technologies [16–19]. Current literature recommends an ideal HR <60 beats/min in order to achieve both optimal image quality and reduction of radiation exposure [20]. Drugs used to lower HR include in this context beta-blockers, calcium-antagonists and more recently ivabradine [21,22]. Premedication with beta-blockers represents the first-line

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option for reduction of HR prior to CTCA examination [23–25]. The use of ivabradine, a novel HR lowering agent, seems to be an attractive option [26,27].

The main aim of this study was to assess whether oral premedication with ivabradine 7.5 mg in patients referred for CTCA is safe and can significantly increase the rate of patients achieving the target HR (<60 bpm) during the exam as compared to ivabradine 5 mg and to chronic beta-blockade treatment.

2. Methods

2.1. Study population

A total of 259 consecutive patients referred for CTCA for the evaluation of suspected or known CAD were prospectively enrolled between October 2008 and April 2010. The baseline characteristics of these patients are summarized in Table 1. All patients were in normal sinus rhythm. Patients with atrial fibrillation (AF), pacemaker, II- and III-degree atrio-ventricular-block (AV-block), New York Heart Association (NYHA) classes III–IV, impaired renal function (creatinine > 1.5 mg/dl), known allergy to iodinated contrast media, pregnancy, unstable clinical condition, thyroid disease, baseline HR < 60 bpm, left ventricular ejection fraction < 30% (LVEF), blood pressure < 100/70 mm Hg (BP), known arrhythmias, retinal disease, asthma or severe chronic obstructive pulmonary disease (COPD) were excluded from the study.

The Institutional Review Board approved the study. All patients gave a written informed consent.

2.2. Enrollment and heart rate control

Patient enrollment is illustrated in Fig. 1. A total of 339 patients referred for CTCA were prospectively enrolled. Fifty patients (15%) were excluded because of contraindications for both multidetector computed tomography (MDCT) and ivabradine. In addition, HR control was not required in 30 patients because of a baseline HR < 60 bpm. Of the remaining 259 patients, 114 were on chronic beta-blockade therapy. In these patients, therapy was shifted to atenolol 50 mg twice a day for 5 days prior to CTCA in order to grant uniformity to the chronic beta-blockade group and to improve chronic antihypertensive therapy avoiding undesirable blood pressure alteration.

All patients were first assessed in an outpatient visit by an experienced cardiologist (T0). During the first assessment, patients' history and demographics, risk factors, current pharmacological treatment, symptoms, and the indication for CTCA were collected. In addition, HR, BP and a 12-lead electrocardiogram (ECG) were obtained.

This was an open-label, single center study assessing whether oral premedication with ivabradine 7.5 mg in patients referred for CTCA is safe and can significantly increase the rate of patients achieving the target HR < 60 bpm during the exam as compared to ivabradine 5 mg and to chronic beta-blockade treatment. Patients not receiving beta blocker at baseline (group 1) and those with beta blocker therapy (group 2) were enrolled in the study. Each group was randomized into 3 parallel arms with 1:1:1 allocation. Patients who did not receive beta blocker at baseline: underwent CTCA without beta blocker (arm controls, n = 49), received ivabradine at 5 mg dosage (arm IV5 n = 48), or received 7.5 mg ivabradine (arm IV7.5, n = 48). Patients with beta blocker therapy: continued with the prior beta blocker without any dose modification (arm BB n = 38), received ivabradine 5 mg (arm BB IV5, n = 38), or received ivabradine 7.5 mg (arm BB IV7.5, n = 38). The duration of premedication was twice a day for 5 days before CTCA. The time interval between the outpatient visit (T0) and the arrival of patient to the scan room (T1) was variable, ranging from 7 to 30 days, depending on the availability of the scanner.

Patients with known history of allergy to drugs (n = 6) were treated with antihistaminic and cortisone therapy starting the day before CTCA.

In all patients arriving in the CT room, HR, BP and a 12-lead ECG were obtained (T1). Intravenous (IV) beta-blockers (atenolol 5 mg up to 15 mg) were administered to all patients with a HR > 60 bpm or when the HR was not consistently <60 bpm during a test breath-hold performed prior to CTCA. Continuous monitoring of HR and ECG was also performed during the CTCA examination (T2). The target HR was defined as an HR constantly <60 bpm.

2.3. CTCA protocol

CTCA was performed with a 64-slice scanner (Aquilion 64, Toshiba, Japan). Prior to CTCA, an unenhanced CT scan was performed in all patients with the aim of quantifying coronary artery calcium (CAC). The parameters for the unenhanced CT study were: gantry rotation time 400 ms, tube voltage 120 kV, tube current 300 mA s, slice thickness 3 mm, reconstruction increment 1.5 mm, field of view 160–180 mm (FOV), and convolution kernel medium. For CTCA the following parameters were used: slices/rotation 64, individual detector width 0.5 mm, gantry rotation time 400 ms, pitch 0.225, tube voltage 120 kV, tube current 500 mA s, reconstruction increment 0.4 mm, FOV 160–180 mm, and convolution kernel medium.

A dose of 80–100 ml of non-ionic iodinated contrast material (iomeprol, Iomeron 400 mgI/ml, Bracco, Milan, Italy) was administered at a rate of 5 ml/s with a power injector (Ulrich Medical, Missouri, USA) attached to an 18-gauge needle positioned in an anti-cubital vein. With the aim of optimizing coronary artery enhancement, the bolus tracking technique was used to synchronize the arrival of contrast material in the coronary arteries with the initiation of the scan. Images were obtained during a single breath-hold of 5–6 s.

Retrospective reconstructions were performed based on the ECG signal to obtain images unaffected by motion artifacts. The time windows used were the mid-to-end diastolic phases (from 60% to 80% of the R–R interval). When performed (e.g. in the case of persistent and residual heart movement reducing the diagnostic quality of the image), additional reconstructions were analyzed generally between 25% and 35% of the R–R interval. Then, images were transferred to a remote dedicated workstation (Vitrea, Vital Images, Plymouth, Minnesota, USA) for post-processing.

2.4. Safety

HR, BP and ECG were continuously monitored during the CTCA examination. Patients with an impaired renal function (creatinine levels between 1.0 and 1.5 mg/dl) were pre-hydrated with 500 ml of saline solution infused in 1 h. The safety of ivabradine was evaluated by monitoring the side effects by phone during the treatment starting 5 days prior to CTCA and for 7 days after its withdrawal.

2.5. Statistical analysis

A central randomization plan was used to facilitate effective randomization and allocation concealment. Standard programming techniques were used for generating the randomization schedule. The randomization scheme involved a block randomization technique with block size of 6. Patients were randomly assigned within the block based on 1:1:1 allocation ratio. The randomization sequence was computer generated.

All continuous variables are presented as mean ± standard deviation, categorical variables as percentages. The paired Student's *t*-test was used to assess differences in continuous variables, unpaired Student's *t*-test and ANOVA for repeated measures, and χ^2 test to assess differences for categorical variables. The Pearson's test was used for correlation analysis. Logistic regression was used to identify significant predictors in achieving target heart rate; multivariable stepwise forward analysis was used for testing variables significant at univariate analysis. All tests were 2-sided, and a value of $p < 0.05$ was considered as significant.

3. Results

CTCA was successfully performed in all patients and no adverse reactions to contrast medium occurred during or after CTCA. Results are summarized in Table 2.

Table 1
Patients characteristics.

	All (n. 259)	Controls (n. 49)	BB (n. 38)	IV5 (n. 48)	IV7.5 (n. 48)	BB + IV5 (n. 38)	BB + IV7.5 (n. 38)	p
Age (yrs)	60.6 ± 10.4	61.6 ± 12.4	63.9 ± 8.8	58.6 ± 7.8	59.6 ± 10.1	59.6 ± 10.9	58.1 ± 9.9	n.s.
Male (%)	62%	71%	63%	60%	44%	63%	53%	n.s.
BMI	28.5 ± 5.8	28.1 ± 5.0	27.8 ± 4.0	27.9 ± 3.8	29.8 ± 9.7	30.0 ± 6.0	27.4 ± 4.0	n.s.
Diabetes	31%	39%	24%	23%	25%	37%	42%	n.s.
Hypertension	85%	73%	95%	83%	83%	95%	95%	<0.01
Dyslipidemia	71%	71%	63%	73%	77%	68%	74%	n.s.
Prior AMI	15%	12%	29%	4%	2%	24%	21%	n.s.
Prior PCI	10%	8%	8%	12%	2%	16%	16%	n.s.
Prior CABG	7%	2%	16%	2%	0%	11%	21%	n.s.
LVEF (%)	55.1 ± 6.2	55.0 ± 5.8	53.0 ± 8.2	56.4 ± 5.8	57.2 ± 5.3	53.7 ± 5.6	55.1 ± 4.6	n.s.

Abbreviations: BMI = body mass index; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; n.s. = not significant.