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Efficacy of ivabradin to reduce heart rate prior to coronary CT angiography: comparison with beta-blocker

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PURPOSE
The objective of our study was to assess the effect of ivabradine on image quality of ECG-gated multidetector computed tomography (MDCT) coronary angiography.

MATERIALS AND METHODS
Computed tomography coronary angiography (CTCA) was performed on two groups. In Group 1 (n=54), an intravenous beta-blocker was administered to patients with a heart rate >70 beats per minute (bpm) just before CTCA. In Group 2 (n=56), oral ivabradine 5 mg was administered twice a day for three days prior to CTCA examination to patients with a heart rate >70 bpm and contraindication to beta-blockers. Images acquired on two different MDCT scanners were scored in terms of image quality of the coronary artery segments using a 5-point grading scale (Grade 1, unreadable; Grade 5, excellent).

RESULTS
The mean heart rates during CTCA were 64±6.7 bpm for Group 1 and 59±4.1 bpm for Group 2 ($P < 0.05$). Mean heart rate reduction was 9±5% and 14±8% for Groups 1 and 2, respectively ($P < 0.001$). A total of 880 segments were evaluated in 110 patients. When the best reconstruction interval was used, 89.8% and 95.5% of all the coronary segments showed acceptable image quality in Groups 1 and 2, respectively. Acceptable image quality of the middle right coronary artery was obtained in 78.3% of Group 1 and 92.4% of Group 2. These ratios for the other segments were 88.4% for Group 1 and 95.2% for Group 2.

CONCLUSION
Reduction of heart rates with ivabradine premedication improves the image quality of CTCA. It should be considered as an alternative drug, particularly in patients with contraindications to beta-blockers.

Key words: • *ivabradine* • *heart rate* • *multidetector computed tomography* • *coronary angiography*

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The rapid technological development of computed tomography coronary angiography (CTCA) over the past decade has significantly increased our ability to image the heart and coronary arteries noninvasively. Essential to performing a successful CTCA examination is obtaining adequate image quality, which depends on a low and stable heart rate and motion-free heart. Despite significant technical advances, such as using 64-row and 320-row CTCA, heart rate control remains an important factor in optimizing the image quality of CTCA (1). Thus, to achieve heart rate reduction, beta-blocking medication or calcium antagonists are routinely administered prior to CTCA examinations. The use of beta-blockers is limited, however, due to contraindications; in recent studies, a substantial portion of patients requiring heart rate reduction have contraindications to beta-blockers (1, 2). Thus, there exists a need for alternative heart-rate-lowering premedication. Ivabradine is a promising heart-rate-lowering agent that reduces the heart's natural pacemaker activity by inhibiting the funny ion (I_f) channel (3). In a recent study, Pichler et al. (4) has compared ivabradine and metoprolol and found that heart rate reduction was significantly more in patients treated with ivabradine than patients receiving long-term beta-blocker therapy.

The aim of the present study was to assess the effectiveness of ivabradine on heart rate reduction and improving image quality of ECG-gated multidetector computed tomography (MDCT) coronary angiography.

Materials and methods

The study group included 110 consecutive patients (25 females, 85 males; mean age, 59±13.8 years; age range, 33–78 years) with suspected coronary artery disease. The study was approved by the institutional ethics committee, and written informed consent was obtained from all subjects prior to the study. Patient characteristics are summarized in Table 1. The patients were all in sinus rhythm. Patients with atrial fibrillation, II or III degree atrio-ventricular-block, impaired renal function (creatinine >1.5 mg/dL), known allergy to iodinated contrast media, thyroid disease, known arrhythmias, or left ventricular ejection fraction <30% were excluded from the study. Patients who had coronary stents or had previously undergone bypass surgery were also excluded. In addition, cases with premature beats, severe respiratory artifacts or severe calcifications that could hamper image quality were excluded.

A total of 146 patients were referred for CTCA over a period of three months. Twenty-two (15%) were excluded due to the exclusion criteria described above. Fourteen patients had a heart rate below 60 beats per minute (bpm), thus premedication was not required. Eleven of the remaining patients (10%) had contraindications to beta-blockers, such as asthma and severe chronic obstructive pulmonary disease, and these

Table 1. Patient characteristics by premedication groups

	Total	Beta-blocker	Ivabradine
Patients, n	110	54	56
Age (years), mean±SD	59±13	63±11	61±8
Male gender, n (%)	87 (78)	43 (80)	44 (79)
BMI (kg/m^2), mean±SD	28±5	29±6	28±4

BMI, body mass index; SD, standard deviation.

patients were treated with ivabradine premedication. Intravenous beta-blocker premedication was administered to 10 (10%) of the remaining patients who had chronic beta-blocker treatment. The remaining 89 patients were randomized to two groups: in Group 1 (n=54), an intravenous beta-blocker (metoprolol, 5 mg/mL bolus) was administered to patients with a heart rate >70 bpm; in Group 2 (n=56), oral ivabradine 5 mg was administered twice a day for three days prior to the CTCA examination to patients with a heart rate >70 bpm. Coronary angiograms were obtained in 25 (Group 1) and 27 patients (Group 2) using the Aquilion 64-MDCT scanner (Toshiba Medical Systems, Tokyo, Japan). Imaging for the remaining patients was acquired using the LightSpeed VCT 64-MDCT scanner (GE Healthcare, Milwaukee, Wisconsin, USA).

CTCA was performed using either scanner with patients in the supine position. An anteroposterior scout image (120 kV, 50 mAs) was first performed to determine the boundaries of the heart. Computed tomography (CT) scans were obtained from 1 cm below the carina to the diaphragmatic face of the heart during a single breath-holding period (6–9 s). The following parameters were used for both scanners: retrospective ECG gating; 912-channel detectors along the gantry and 64-channel detectors along the z-axis; tube voltage 120 kV; tube current 550–750 mA (depending on patient size); and scan field of view (SFOV) 50 cm. Gantry rotation, slice width, and helical pitch parameters were as follows: 0.40 s/rotation (for two scanners); 0.625 mm and 0.5 mm; and 0.18–0.24 and 0.2; for the first and second scanners, respectively. Ninety milliliters of iodinated contrast medium (Omnipaque 350, Amersham Health, Cork, Ireland) were injected intravenously at 5 mL/s, followed by 40 mL saline at 2.5 mL/s.

Retrospective ECG-gated reconstructions were performed between the levels containing the first several centimeters of the left and right coronary arteries. The best reconstruction window was then selected, and ECG-gated reconstruction was performed for whole axial resource images. The reconstructed images were then transferred to a post-processing workstation (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA; Hewlett-Packard xw8200 workstation with dual Xeon processors and 4 GB of RAM, GE Healthcare, Waukesha, Wisconsin, USA) for further analysis with specialized software. Axial source, multiplanar reconstruction, maximum intensity projection, and volume-rendered images were used for assessment of the coronary arteries. Image quality was assessed by two radiologists who independently reviewed the images without knowledge of the other's interpretations.

The two radiologists independently assessed eight of 15 coronary segments differentiated according to the American Heart Association classification: the left main coronary artery (LMCA); the proximal and middle segments of the left anterior descending (LAD) and left circumflex (LCX) coronary arteries; and the proximal, middle, and distal segments of the right coronary artery (RCA). A 5-point scale was used to assess the image quality of each coronary segment: 5, no motion artifacts; 4, minor artifacts (mild blurring); 3, moderate artifacts (moderate blurring without discontinuity); 2, severe artifacts (doubling or discontinuity in the course of the coronary segments); and 1, unreadable (vessel structures not differentiable) (Fig.). A score of 4 or higher was considered acceptable image quality. The number of patients with acceptable image quality in each coronary segment was calculated, and the results were compared between the two groups.

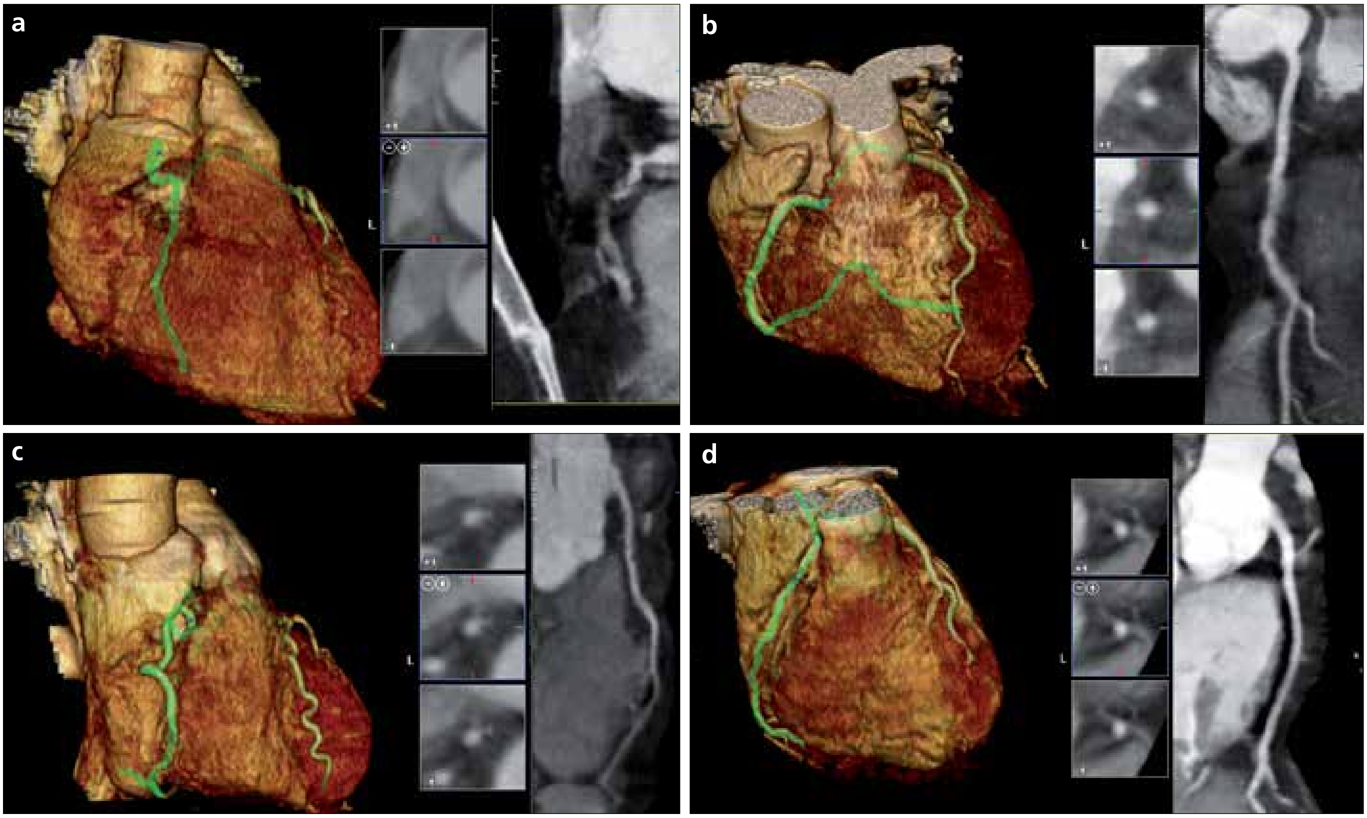
Statistical analysis

Statistical analysis was performed using a commercially available software (Statistical Package for Social Sciences, version 16, SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as the mean value±standard deviation. Categorical variables are presented as absolute number (percentage). Inter-observer agreement for image quality and best reconstruction interval readout were calculated with Cohen's κ statistics. Pearson's correlation analysis was performed to compare the image quality scores of all segments together and the scores for separate arteries (RCA, LMCA, LAD, and LCX) with the average heart rate and its standard deviation during CT scanning. A P value of less than 0.05 indicated a statistically significant difference.

Results

All subjects had a sinus rhythm on ECG during CT. The mean heart rate prior to CTCA was 71±9.8 bpm for Group 1 and 65±7.8 bpm for Group 2. The mean heart rate during CTCA was 64±6.7 bpm for Group 1 and 59±4.1 bpm for Group 2 ($P < 0.05$). Mean heart rate reduction was 9±5% and 14±8% for Groups 1 and 2, respectively ($P < 0.001$) (Table 2). Coronary artery stenosis was detected in two patients in Group 1 and four patients in Group 2 on CTCA. A total of 880 segments were evaluated in 110 patients. When the best reconstruction interval was used, 89.8% and 95.5% of all the coronary segments showed acceptable image quality in Groups 1 and 2, respectively. Acceptable image quality of the middle RCA was obtained in 78.3% of Group 1 and 92.4% of Group 2. These ratios for the other segments were 88.4% and 95.2% for Groups 1 and 2, respectively. Table 3 shows the percentage of patients with images of acceptable quality (score 4 or more) of each coronary segment. Table 4 shows the distribution of image quality scores of the 880 segments for both reviewers.

The 60%–70% reconstruction interval in the cardiac cycle was judged by both reviewers to provide the best image quality for assessing the coronary arteries in both groups. Inter-observer



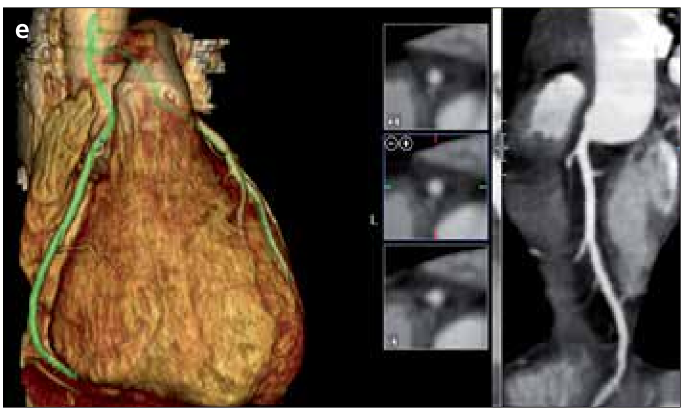


Figure. a–e. CT coronary angiograms show middle segment of right coronary artery. The vessel structure is not visible (Grade 1) **(a)**. The doubling and discontinuity in the course of coronary segments are seen (Grade 2) **(b)**. Moderate blurring of vascular margin is marked (Grade 3) **(c)**. Mild blurring of vascular margin (Grade 4) **(d)** and little motion artifact (Grade 5) **(e)** are seen.

Table 2. Mean heart rates by premedication groups

	Total	Beta-blocker	Ivabradine
Admission heart rate (bpm)	73±7.2	75±4.8	73±5.8
Heart rate prior to CTCA (bpm)	68±8.1	71±9.8	65±7.8
Heart rate during CTCA (bpm)	62±8.5	64±6.7	59±4.1
Heart rate reduction rate (%)	11±7%	9±5%	14±8%

bpm, beats per minute; CTCA, computed tomography coronary angiography.
Data are presented as mean±SD.

agreement for image quality rating was good (κ=0.70).

Postural hypotension occurred in one patient in Group 1 and two patients in Group 2. Local or minor systemic allergic reactions to contrast material, such as skin rashes, developed in two patients in Group 1 and three patients in Group 2. One patient had transient blurred vision before CTCA.

Discussion

The rapid improvement of MDCT technology has provided higher quality imaging and greater diagnostic accuracy for the evaluation of coronary artery disease. Despite significant technical advances, however, heart rate control remains an important issue in optimizing image quality, even with 64-row and 320-row CTCA. A target heart rate of 60 bpm or lower provides optimum image quality, with a heart rate of 65 bpm or lower providing good image quality in most cases (5, 6).

A lower heart rate reduces coronary artery movement artifacts by increasing the length of the diastolic phase and effectively increasing the time that the coronary arteries are motion-free. In particular, the RCA and the LCX artery are more prone to motion artifacts, due to close proximity to the right and left atria, respectively (7–10). Graaf et al. (1) and Shapiro et al. (2) found that approximately half of the patients in their series required

Table 3. Percentages of patients with acceptable image quality in each coronary segment

	Coronary segment							
		LAD		LCX		RCA		
	LMCA	Proximal	Middle	Proximal	Middle	Proximal	Middle	Distal
Beta-blocker (n=54)	95%	96%	92%	90%	89%	88%	78%	91%
Ivabradine (n=56)	100%	100%	100%	100%	92%	94%	92%	93%

LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; RCA, right coronary artery.

Table 4. Distribution of image quality scores of 880 segments for both reviewers

	Number (%) of segments			
	Beta-blocker		Ivabradine	
Score	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
1	7 (2.4)	9 (3.1)	2 (0.6)	4 (1.2)
2	3 (1.0)	5 (1.7)	0	1 (0.3)
3	22 (7.6)	18 (6.2)	14 (4.3)	12 (3.7)
4	25 (8.6)	27 (9.3)	19 (5.9)	22 (6.8)
5	231 (80.2)	229 (79.5)	285 (89.0)	282 (88.1)

heart rate reduction before CTCA. Although improved temporal resolution, with a decrease in total scanning time, and improved longitudinal resolution have enabled image quality to become less dependent on heart rate, a clear relation between image quality and increased heart rate has been demonstrated, using 64-row and 320-row CTCA (1). In addition, Rybicki et al. (11) found that the most common cause of image degradation was cardiac motion when using 320-row CTCA.

Beta-blockers are generally used to achieve short-term heart rate reduction for CTCA. In the study by Graaf et al., (1) the target heart rate for CTCA was achieved with beta blockade in 73% of patients. Maffei et al. (12) concluded that heart rate control might be most adequately provided by intravenous beta-blockers without nitrates, with a mean heart rate reduction of 16±8 bpm. In contrast, Shapiro et al. (2) reported that the target heart rate was reached in only 35% of the patients receiving beta-blocker before CTCA. The use of beta-blockers is also limited due to contraindications, such as severe aortic stenosis, asthma, severe chronic obstructive pulmonary disease with significant bronchospasm, severe peripheral vascular disease (with claudication), overt heart failure, sick sinus syndrome, second/third-degree heart block, and treatment with verapamil. In recent studies, contraindications to beta-blockers were present in a substantial portion of patients requiring heart rate reduction (1, 2). In the present study, 11 patients (10%) had contraindications to beta-blockers. These observations have prompted physicians to search for alternative heart rate-lowering premedication.

Calcium channel blockers (diltiazem and verapamil) can be used to slow the heart rate for cardiac imaging, particularly when beta-blockers are contraindicated (13). In practice, however, the reduction rate efficiency of these drugs has been disappointing (14). Furthermore, they are contraindicated in patients with a history of heart failure or significantly impaired left ventricle function.

Ivabradine is a selective inhibitor of the I_f channel that reduces heart rate in the sinus node. Therefore, it is useful in patients in sinus rhythm (3). Ivabradine, classified as a cardiotonic agent, is indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication to or intolerance to beta-blockers. Coronary blood flow velocity increases after ivabradine treatment, because the diastolic period is prolonged (per cardiac beat and per minute), as expected. In addition, enhanced diastolic relaxation may possibly increase early diastolic coronary blood flow by a "suction effect" (15). Ivabradine is generally well tolerated, but patients may complain of some side effects, such as visual symptoms and bradycardia. Ivabradine is contraindicated in severe bradycardia, II or III degree atrio-ventricular block, ejection fraction <35%, and severe hypotension (16). In addition, it should not be used in patients who are already taking CYP 3A4 inhibitors, such as ketoconazole, macrolides (such as erythromycin), and nefazodone (used in the treatment of human immunodeficiency virus) (3).

In the study by Pichler et al. (4) comparing two groups of oral premedication with ivabradine 15 mg or metoprolol 50 mg, no significant differences were found in the reduction of heart rate, but in subgroups receiving long-term beta-blocker therapy, significantly stronger heart rate reduction was achieved with ivabradine (4). In the study by Guaricci et al., (16) the combination of both ivabradine and beta-blocker yielded the best results in terms of heart rate reduction and rate of patients achieving the target heart rate compared to control, beta-blocker, and ivabradine groups. The mean relative heart rate reduction between admission and CTCA was 14.7±7.1% for controls, 12.0±10.2% for the chronic beta-blocker treatment group, 18.6±9.6% for the ivabradine group, and 24.0±10.4% for the chronic beta-blocker treatment and ivabradine group (for trend $P < 0.001$). In their study, ivabradine premedication significantly reduced heart rate prior to CTCA, and administration of ivabradine improved the rate of patients achieving the target heart rate of <65 bpm during CTCA compared to chronic beta-blocker therapy. Similarly, in the present study, compared to the beta-blocker group, heart rate control was more adequately provided in the ivabradine group, with a mean heart rate of 59±4.1 bpm. In addition, CTCA image quality improved in the group treated with ivabradine premedication, which produced 95.5% diagnostically acceptable coronary segments compared to 89.8% with beta-blocker premedication. In our study, image quality of the middle portion of the RCA and the LCX artery was lower than that of the other segments, due to their close proximity to the right and left atria, respectively. The LMCA and LAD arteries follow left ventricular motion, but their velocity of motion is significantly lower than that of the RCA and the LCX artery, so high-quality images of the LMCA and LAD arteries could likely be obtained at higher heart rates (7, 17, 18).

Our study had several limitations. First, the study population was relatively small, and although the differences between groups were significant, further studies with larger series are required to confirm our results. Second, because of the contraindications, patient population selection was highly limited. Third, heart rate variability was not evaluated in our study. We also did not include coronary artery stenosis detection, which may have been biased due to an incomplete data set. In addition, a relative disadvantage of oral ivabradine premedication is a delay time of approximately three days; however, this only becomes an issue in urgent cases.

In conclusion, our study indicates that CTCA with oral ivabradine premedication is feasible, and a safe and effective way of reducing heart rate to generate images of diagnostically acceptable quality in almost all coronary segments. Thus, ivabradine can successfully substitute for beta-blockers, particularly in patients with contraindications to beta-blockers.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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