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Safety and Efficacy of a Bolus Injection of Landiolol Hydrochloride as a Premedication for Multidetector-Row Computed Tomography Coronary Angiography

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Background: We evaluated the safety and efficacy of a bolus injection of landiolol hydrochloride, an ultrashort-acting β1-selective antagonist, as an additional treatment after premedication with an oral β-blocker to reduce heart rate prior to multidetector-row computed tomography (MDCT) coronary angiography (CAG).

Methods and Results: A total of 458 patients who underwent MDCT CAG were retrospectively enrolled. Image quality and hemodynamic parameters were compared in patients before and after approval of landiolol hydrochloride. If heart rate reduction was insufficient after premedication with an oral β-blocker, a bolus injection of landiolol hydrochloride (n=66) or other drugs (n=30) was used. The percentage of evaluable images per segment in patients after approval of landiolol (99.3%) was greater than that in patients before approval of landiolol (97.4%, P<0.01). Heart rates before scanning in patients receiving landiolol hydrochloride were similar to those receiving other drugs. Heart rate was significantly reduced approximately 5 min after injection of landiolol hydrochloride and increased shortly. No decrease in systolic blood pressure or other adverse effects was observed.

Conclusions: Bolus injection of landiolol hydrochloride sufficiently reduced heart rate without significantly reducing systolic blood pressure and produced a high percentage of evaluable images, suggesting that bolus injection of landiolol hydrochloride as an additional pretreatment is feasible in MDCT CAG. (*Circ J* 2013; **77:** 146–152)

Key Words: β-blocker; Coronary angiography; Landiolol; Multidetector-row computed tomography

Multidetector-row computed tomography (MDCT) is a promising noninvasive coronary imaging modality for visualizing coronary atherosclerosis in patients with known or suspected coronary artery disease.[1–4] However, a high heart rate (HR) can produce motion artifacts that reduce image quality.[1] Oral β-blockers have been widely used as premedication to reduce the HR to a level suitable for MDCT coronary angiography (CAG).[5] When oral β-blockers are not sufficient, intravenous β-blockers or other medications are sometimes used to further reduce the HR. However, side effects from additional premedications are common and can be life-threatening, because of prolonged pharmacologic effects.

Landiolol hydrochloride, an ultrashort-acting β1-selective antagonist, exerts a clinically relevant negative chronotropic action without negative inotropic effects when given at a low dose.[6,7] It can be used safely to reduce a patient's HR, as shown by recent clinical studies.[8–13] In addition, a previous study showed the usefulness of continuous infusion of landiolol hydrochloride for reducing HR before MDCT CAG.[14] Landiolol hydrochloride became available in Japan in September 2011 as a premedication for reducing HR for MDCT CAG, so the side effects and efficacy of landiolol hydrochloride for MDCT angiography in real clinical settings in Japan have not been fully elucidated.

To address these issues, we investigated the safety and efficacy of reducing HR with a single bolus injection of landiolol hydrochloride in combination with oral β-blocker administration prior to MDCT CAG.

Methods

Study Population

The study population included a total of 458 consecutive pa-

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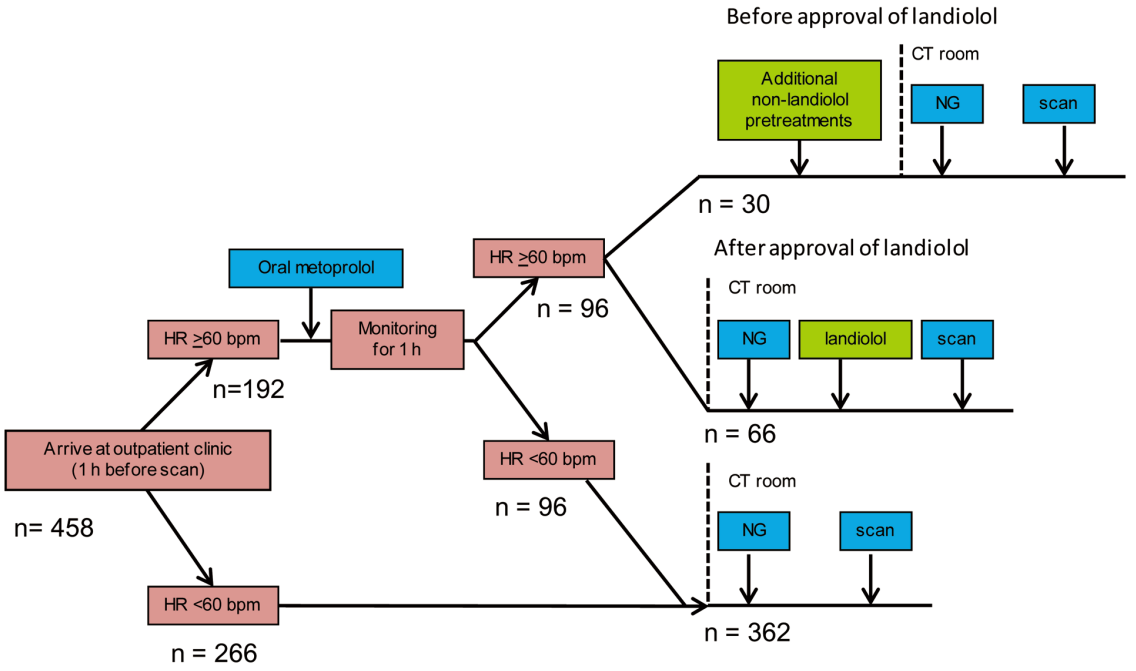

Figure 1. Diagram of steps involved in MDCT coronary angiography. All patients arrived at the hospital 1 h before the scheduled scanning time. All patients whose heart rate was ≥60 beats/min received oral metoprolol (20–40 mg). Before the approval of landiolol, if heart rate was still ≥60 beats/min, patients received an additional 20 mg oral metoprolol and/or 2 mg intravenous propranolol and/or 5 mg intravenous verapamil as additional pretreatments, repeated as needed to achieve a suitable heart rate. After approval of landiolol, patients received a bolus injection of landiolol hydrochloride (0.125 mg/kg) as additional pretreatment. HR, heart rate; bpm, beats/min; CT, computed tomography; NG, nitroglycerin.

tients who visited Okayama University Hospital or Tsuyama Central Hospital between January 2011 and February 2012 for 64-slice MDCT examination because of suspected coronary artery disease. Patients with any heart rhythm other than sinus rhythm, with any contraindication for β-blockers, or an inability to hold their breath on command were excluded. Patients with previous myocardial infarction or those with coronary stents were included, but patients who had undergone coronary artery bypass graft surgery were excluded. This study was approved by the institutional ethics committee on human research and written informed consent was given by all patients before the study.

Patient Preparation

Landiolol hydrochloride (Corebeta, Ono Pharmaceutical Co, Osaka, Japan) was approved in November 2011 for use at Okayama University Hospital and in December 2011 for use at Tsuyama Central Hospital. The study participants were divided into 2 groups: those examined before landiolol was approved (n=229) and those examined after landiolol was approved (n=229). A diagram of the study protocol is shown in Figure 1. All patients arrived at the hospital 1 h before the scheduled scanning time, and those who showed a persistently high HR of ≥60 beats/min received oral metoprolol (20–40 mg). If the HR was not sufficiently lowered (<60 beats/min) before the scheduled scanning time, patients who were treated prior to landiolol approval received additional oral metoprolol (20 mg; n=22) and/or 2 mg intravenous propranolol (n=8) and/or 5 mg intravenous verapamil (n=9) as additional pretreatments. After approval of landiolol, patients received a bolus injection of landiolol hydrochloride at a dose of 0.125 mg/kg as an additional pretreatment if the HR was not sufficiently lowered. Landiolol hydrochloride was injected intravenously 4–7 min before starting MDCT. Additional premedication was given to 30 patients before approval of landiolol and 66 patients after approval of landiolol.

Data Acquisition

The 64-slice CT scans were obtained using a DCT scanner (Okayama University Hospital: SOMATOM Definition Flash, Siemens Medical Solutions, Germany; Tsuyama Central Hospital: LightSpeed VCT, GE Healthcare, USA). SOMATOM Definition Flash parameters were as follows: detector collimation 64×0.6 mm, equaling a slice acquisition of 128×0.6 mm using the flying focal spot technique; table pitch adapted to HR (0.17–0.38); rotation time 275 ms; tube current time product 360 mA; and tube voltage 120 kVp. LightSpeed VCT parameters were: rotation time 350 ms; pitch 0.516 mm per gantry rotation; helical acquisition mode; detector configuration 64 rows with 0.625-mm-thick sections; and tube voltage 120 kVp. At Okayama University Hospital, a test bolus CT acquisition was performed at the level of the ascending aorta following administration of 10 ml contrast medium followed by 20 ml saline, with low-dose images obtained every 1 s. The delay before the formal scan was calculated as the time to peak enhancement in the ascending aorta plus 3 s to ensure enhancement of the distal segments of the coronary arteries. For the final scan, contrast agents (Omnipaque 350, Daiichi

Table 1. Characteristics of Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol		After approval of landiolol	
	All (n=229)	Patients receiving additional pretreatments (n=30)	All (n=229)	Patients receiving landiolol (n=66)
Age (years)	67±12	67±12	66±14	66±13
Men	117 (51%)	15 (50%)	127 (56%)	32 (49%)
BMI (kg/m^2)	22.9±3.8	22.6±3.6	22.9±3.6	22.3±3.0
Hypertension	126 (55%)	15 (50%)	140 (61%)	39 (59%)
Hyperlipidemia	138 (60%)	14 (47%)	91 (40%)*	25 (38%)
Diabetes mellitus	66 (29%)	11 (37%)	58 (25%)	21 (32%)
Angina pectoris	52 (23%)	6 (20%)	41 (18%)	12 (18%)
Prior MI	10 (4%)	1 (3%)	7 (3%)	2 (3%)
History of stent implantation	15 (7%)	1 (3%)	9 (4%)	1 (2%)
Medications				
β-blocker	26 (11%)	2 (7%)	21 (9%)	3 (4.5%)
CCB	66 (29%)	11 (37%)	79 (35%)	25 (38%)
ACEI/ARB	71 (31%)	7 (23%)	93 (41%)†	27 (41%)

Values represent mean±SD or number (%). *P<0.05 vs. all patients before approval of landiolol; †P<0.05 vs. all patients after approval of landiolol.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAG, coronary angiography; CCB, calcium-channel blocker; MDCT, multidetector-row computed tomography; MI, myocardial infarction.

Sankyo, Japan) were injected over 10 s, followed by a second bolus of 80% of the amount of contrast medium diluted 50%, and then a chaser bolus of saline. All injections were done at the same flow rate, calculated as body weight ×0.07 ml/s. At Tsuyama Central Hospital, the test bolus tracking method was performed. The amount of contrast material (Iopamiron 370, Bayer, Germany) was calculated as 330 mgI/kg. The flow time was fixed at 15 s, and the flow rate was calculated accordingly. A test bolus was performed with 5 ml contrast material followed by 20 ml saline at the same flow rate. The main injection was performed continuously at the same flow rate followed by 20 ml saline.

Axial slices were optimally reconstructed within the mid- to end-diastolic phase in each patient using retrospective ECG gating[15] and commercially available cardiac reconstruction software (AZE Inc, Tokyo, Japan). Three postprocessing techniques were applied to assess the coronary arteries: (1) maximum intensity projection, (2) curved multiplanar reconstruction, and (3) volume rendering. One senior cardiologist and 2 senior CT technicians performed the analysis, and evaluation was made on a per-segment basis. Sixteen segments were identified based on the established American Heart Association segment model[16] and consisted of the right coronary artery and distal branches (5 segments), left main trunk (1 segment), left main anterior descending artery and branches (5 segments), and circumflex artery and branches (5 segments). Segments that were absent or too small, or that contained heavy calcification or a stent, were excluded. Each segment was classified as evaluable or not evaluable as described.[17–19] Non-evaluable images were defined as those with no vessel wall definition owing to marked motion artifacts, significant structural discontinuity, or high image noise-related blurring that precluded the acquisition of diagnostic information. Segments that could be evaluated included those with excellent, good, or fair quality. Images with excellent quality were defined as those with no motion artifacts, noise-related blurring, or structural discontinuity. Images with good quality were defined as those with only minor motion artifacts or noise-related blurring and no structural discontinuity. Images with fair quality were those with some motion artifacts, noise-related blurring, or minimal structural discontinuity. Image quality was evaluated by 2 experienced observers who had no knowledge of pretreatments for reducing HR for MDCT CAG. The interobserver coefficient of variation analyzed from 20 randomly selected samples was <5%.

Evaluation of Adverse Effects of Additional Treatment

Hemodynamic parameters (systolic blood pressure (BP), diastolic BP, and HR) were evaluated for all patients upon entry into the CT room and immediately before and after scanning. For patients treated with landiolol hydrochloride, additional measurements were taken before the bolus injection. Potential adverse effects of landiolol hydrochloride (hypotension, floating sensation, dizziness, serious bradycardia, and cardiogenic shock) were also assessed by nurses.

Statistical Analysis

Continuous variables are presented as the mean±SD, and differences between the 2 groups were evaluated using an unpaired t-test. Categorical variables are presented as frequencies, and intergroup comparisons were analyzed using the χ^2 test. One-way ANOVA was performed followed by a post-hoc Bonferroni test to examine differences in the time course of hemodynamic changes. A P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Clinical characteristics of the 458 enrolled patients are summarized in Table 1. Our study included 244 men (53%) with a mean age of 66 years. Patients seen before approval of landiolol had a greater prevalence of dyslipidemia, but the prevalence of hypertension and of diabetes mellitus was com-

Table 2. Quality of Images Obtained Per Segment, Per Artery, and Per Patient in Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol	After approval of landiolol	P value
In all patients			
n	229	229	
Per segment	3,237/3,310 (97.8%)	3,333/3,383 (98.5%)	0.03
Per artery			
LMT	229/229 (100%)	229/229 (100%)	1
LAD	201/229 (87.8%)	217/229 (94.8%)	<0.01
LCX	213/229 (93.0%)	217/229 (94.8%)	0.44
RCA	208/229 (90.8%)	217/229 (94.8%)	0.10
Per patient	182/229 (79.4%)	203/229 (88.6%)	<0.01
In patients who received additional pretreatment			
n	30	66	
Per segment	418/429 (97.4%)	985/992 (99.3%)	<0.01
Per artery			
LMT	30/30 (100%)	66/66 (100%)	1
LAD	27/30 (90%)	66/66 (100%)	<0.01
LCX	28/30 (93.3%)	63/66 (95.5%)	0.66
RCA	26/30 (86.7%)	62/66 (93.9%)	0.23
Per patient	23/30 (76.7%)	62/66 (93.9%)	0.01

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; RCA right coronary artery. Other abbreviations as in Table 1.

Table 3. Hemodynamic Parameters in Patients Who Received Additional Pretreatments Among Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol (n=30)	After approval of landiolol (n=66)	P value
At outpatient clinic			
SBP (mmHg)	144±16	135±19	0.05
DBP (mmHg)	84±12	81±13	0.33
HR (beats/min)	89±12	78±10	<0.01
Before the additional pretreatment			
SBP (mmHg)	129±16	122±19	0.09
DBP (mmHg)	78±12	72±13	0.02
HR (beats/min)	77±12	76±10	0.70
At the time of scanning			
SBP (mmHg)	137±19	120±18	<0.01
DBP (mmHg)	77±14	68±12	<0.01
HR (beats/min)	68±9	67±10	0.35
After scanning			
SBP (mmHg)	136±29	127±19	0.02
DBP (mmHg)	77±16	70±13	0.03
HR (beats/min)	66±10	70±10	0.07

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. Other abbreviations as in Table 1.

parable between the 2 groups. Patients after approval of landiolol had a greater use of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers. There were no differences in the prevalence of angina pectoris, prior myocardial infarction, or history of stent implantation between the 2 groups. The dosage of oral metoprolol as an initial pretreatment in patients before approval of landiolol (n=121) was significantly greater than that in patients after approval of landiolol (n=91) (26±10 mg vs. 22±6 mg, P<0.01). Analysis of patients who received additional pretreatment showed no differences in age, sex, body mass index, risk factors, medications, prevalence of angina pectoris, prior myocardial infarction, or history of stent implantation between patients receiving landiolol or those receiving other drugs. The dosage of oral metoprolol tended to be greater in patients receiving other drugs than in patients receiving landiolol, but there was no statistical difference (26±5 mg vs. 21±6 mg, P=0.14).

Table 2 shows the evaluation of image quality in all patients and in those who received additional pretreatments. Among all patients, the percentage of evaluable segments was

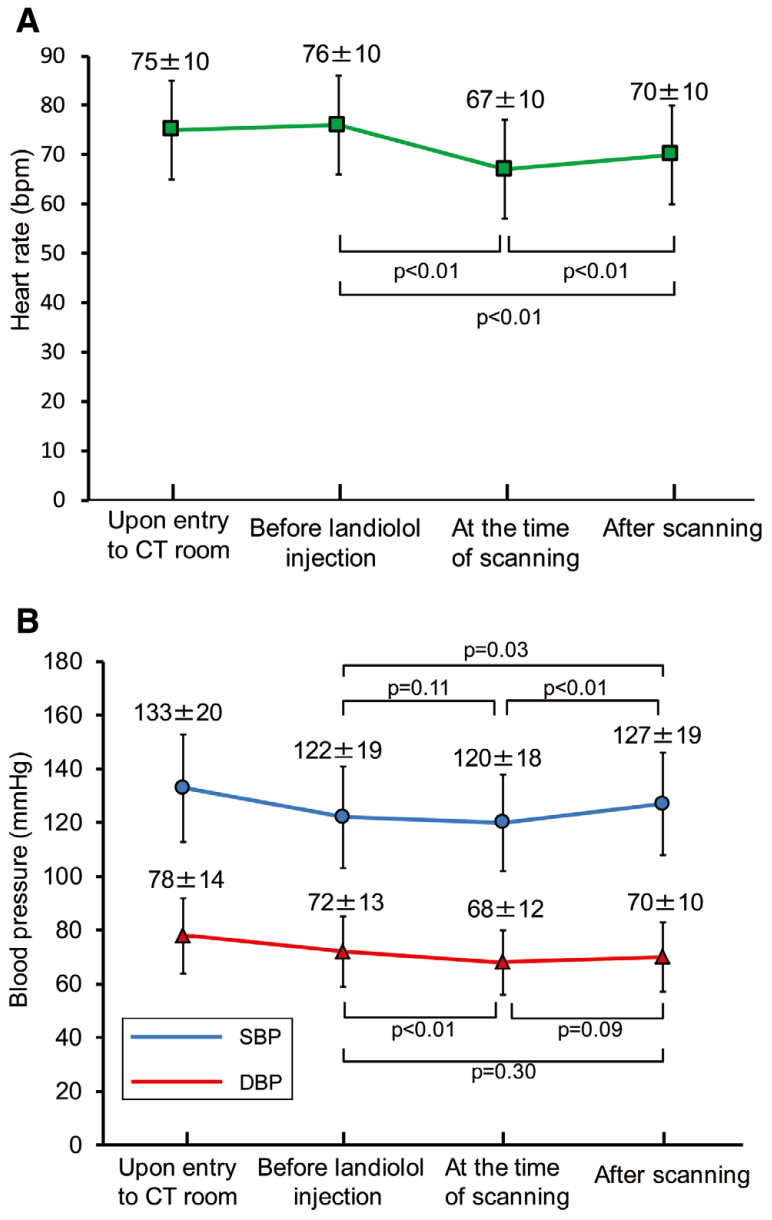

Figure 2. Graph showing the sequential changes in heart rate (**A**) and blood pressure (**B**) immediately after scanning of 66 patients given landiolol upon entry to the CT room. Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

significantly higher after approval of landiolol than before approval of landiolol (98.5% vs. 97.8%, respectively, P=0.03). When image qualities were analyzed according to the left main trunk, left anterior descending artery, left circumflex artery, and right coronary artery, the percentage of evaluable images in the left anterior descending artery was significantly higher after approval of landiolol than before approval of landiolol (94.8% vs. 87.8%, respectively, P<0.01). For patient-based analysis, 203 patients after approval of landiolol and 182 patients before approval of landiolol showed no motion artifacts (88.6% vs. 79.4%, respectively, P<0.01).

In patients who received additional pretreatment, the percentage of evaluable segments was significantly higher after approval of landiolol than before approval of landiolol (99.3% vs. 97.4%, respectively, P<0.01). When image quality was analyzed according to artery, the percentage of evaluable images in the left anterior descending artery was significantly higher after approval of landiolol than before approval of landiolol (100% vs. 90%, respectively, P<0.01). For patient-based analysis, the evaluable percentage was significantly higher after approval of landiolol than before approval of landiolol (93.9% vs. 76.7%, respectively, P=0.01).

Hemodynamic parameters assessed immediately before scanning and after scanning are shown in **Table 3**. HR was significantly higher in patients receiving other drugs than in patients receiving landiolol. HRs just before and after scanning were comparable between patients receiving landiolol and those receiving other drugs. BP just before scanning was significantly lower in patients receiving landiolol than in those receiving other drugs (P<0.01). For patients treated with landiolol (n=66), **Figure 2** shows the time course of BP and HR upon entry to the CT room, before the bolus injection and immediately before and after scanning. HR was significantly decreased before scanning and then significantly increased

after scanning, but did not recover to the same level as before scanning. There were no significant decreases in systolic BP over the same time course. There were no adverse effects from landiolol hydrochloride; however, 1 patient who received 2 mg intravenous propranolol and 5 mg intravenous verapamil developed low BP for which an intravenous hypertensive agent was necessary. The amount of time from the beginning of the visit to the outpatient clinic to the end of the CT scan was significantly shorter in patients after approval of landiolol (n=229) than before approval of landiolol (n=229) (90±13 vs. 159±45 min, respectively, P<0.01).

Discussion

This study revealed that for patients who had an elevated HR after an initial metoprolol dose prior to MDCT CAG, a bolus injection of landiolol hydrochloride was safe and resulted in better image quality that with the conventional protocol without landiolol hydrochloride. This is the first study to demonstrate the clinical applicability of a bolus injection of landiolol hydrochloride as a pretreatment in combination with an oral β-blocker for MDCT CAG.

Cardiac motion artifacts are a major problem in obtaining optimal coronary vessel images during MDCT, and thus HR must be adequately controlled.[20,21] Oral β-blocking agents are widely used to reduce HR, but they are not always sufficient.[22] Landiolol has similar pharmacological properties as esmolol,[23] but is short-acting and highly selective for β1 receptors, thus showing fewer side effects than other longer-acting β-blockers.[6,7] Recent studies have shown landiolol to be safe and effective in patients with perioperative atrial fibrillation or tachycardia,[9,11,13] in patients with severe ventricular arrhythmia[10] or acute decompensated heart failure,[11] and for early initiation of β-blockers in patients with acute myocardial infarction.[12] In addition, Isobe et al reported the usefulness of continuous infusion of landiolol hydrochloride for MDCT CAG.[14] Although continuous infusion of landiolol hydrochloride is reported to be safe,[14] such a procedure seems complicated in an outpatient clinic. Compared with continuous injection, the bolus injection used in this study was more practical. Furthermore, this study showed that only approximately 20% of patients who were scheduled for MDCT CAG required any premedication beyond oral β-blocker treatment. Therefore, the use of landiolol hydrochloride in selected patients may have cost-benefit advantages.

Our study assessed the effect of landiolol hydrochloride on hemodynamics during MDCT CAG. Among the patients imaged before approval of landiolol, 1 developed severe hypotension that required treatment. The protocol using a bolus injection of landiolol hydrochloride produced only a transient reduction in HR and no significant change in systolic BP. Furthermore, the amount of time from the beginning of premedication to the end of the CT scan was strikingly shorter in patients receiving landiolol hydrochloride than in those receiving other additional drugs. Thus, landiolol hydrochloride as an additional pretreatment may be useful in MDCT CAG.

Our study also compared image quality in patients before and after approval of landiolol. Although the image quality was significantly better in patients receiving landiolol hydrochloride than in those receiving other drugs, we believe that the difference was not clinically important. The overall percentage of evaluable images in both groups was 97–99%, which is sufficient for clinical use. Recent studies have shown that the percentage of evaluable images is over 90–95% when the HR is controlled appropriately.[5,21,24] Image quality with MDCT CAG is affected not only by absolute HR, but also by variability in HR.[25] However, we could not examine the difference in HR variability during CT scanning, because no data were available for patients who received additional pretreatments without landiolol. A possible explanation for the improved image quality in patients receiving landiolol hydrochloride is that it reduced HR variability during the CT scan more effectively than other drugs such as verapamil.

Study Limitations

The first limitation of our study is that among the total 458 patients enrolled, only 96 received additional premedication, including landiolol hydrochloride. Therefore, further investigation in a larger population is needed to make solid conclusions regarding the safety of landiolol hydrochloride and image quality in individual patients. Second, in this study, a greater number of patients required additional pretreatment after approval of landiolol than before approval. Although our medical staff strived to follow the protocol, additional pretreatments were not used in some cases before approval of landiolol, especially in patients whose HRs were near 60 beats/min because of concerns about adverse effects of additional β-blocker injection, delay of another scheduled CT, and extension of the patient's examination time. In similar situations after landiolol approval, however, more patients may have been given additional pretreatment because of fewer concerns. It is possible that these factors affected our results. Third, patients with heavily calcified lesions, stents, and bypass grafts were excluded from our analysis. Also, sublingual nitroglycerin was used in all patients. These factors may have affected image quality. However, every assessable arterial branch was included in our analyses, regardless of diameter.

Conclusions

Bolus injection of the ultrashort-acting β-blocker, landiolol hydrochloride, reduced HR to a level suitable for MDCT without causing a significant reduction in BP. Use of landiolol hydrochloride in combination with metoprolol for HR control shortened the total procedure time compared with the use of other secondary drugs, and high-quality images were obtained. Therefore, a bolus injection of landiolol hydrochloride is feasible as an additional premedication for MDCT CAG.

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Disclosures

Conflicts of Interest: The authors declare no conflicts of interest.

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