ORIGINAL RESEARCH ARTICLE

A Multicenter, Open-Label Study of an Intravenous Short-Acting β₁-Adrenergic Receptor Antagonist Landiolol Hydrochloride for Coronary Computed Tomography Angiography by 16-Slice Multi-Detector Computed Tomography in Japanese Patients with Suspected Ischemic Cardiac Disease

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Abstract

Background During coronary computed tomography (CT) angiography (CCTA), β-blockers (β-adrenergic receptor antagonists) have commonly been used to lower heart rate and improve image quality.

Objectives The aim of this study was to investigate the image quality-improving effect as well as the heart rate-lowering effect of landiolol hydrochloride (an intravenous short-acting β₁-adrenergic receptor antagonist) in CCTA by 16-slice multi-detector CT (MDCT).

Methods A total of 39 subjects suspected of having ischemic cardiac disease and requiring CCTA received 0.125 mg/kg of landiolol hydrochloride to study the efficacy and safety of landiolol hydrochloride in a multicenter open-label clinical study. The endpoint was the diagnosable proportion (proportion of subjects whose coronary stenosis was diagnosable).

Results The diagnosable proportions for the reconstruction images at mid-diastole were 56.0 %. The diagnosable proportions for the optimal reconstruction images were 65.4 %. The mean heart rate-lowering effect was observed soon after administration of landiolol hydrochloride; the peak of the effect was reached in 3–5 min, and the effect wore off in 30 min after completion of administration. The mean heart rate-lowering proportion at that time was −14.46 ± 8.4 %.

Conclusions Landiolol hydrochloride was confirmed to reduce heart rate significantly and rapidly after intravenous injection and this suggests that the study drug is a safe and useful agent for improving the image quality of CCTA by 16-slice MDCT.

Members of the Landiolol Hydrochloride Study Group are listed in Appendix.

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Key Points

Heart rate reduction was observed by using landiolol hydrochloride, which then brought decreases in motion artifacts

Landiolol hydrochloride was suggested to be useful for coronary computed tomography (CT) angiography by 16-slice multi-detector CT (MDCT) as well as 64-slice MDCT

1 Introduction

Coronary computed tomographic (CT) angiography (CCTA) is being used as a non-invasive method for diagnosing the existence or non-existence of coronary stenosis and also its location [1, 2]. In single and multicenter studies [3, 4], CCTA has been shown to be useful with its very high negative predictive value. However, it has been reported that CT image quality is lowered in patients with a high heart rate, requiring administration of β-blockers (β-adrenergic receptor antagonists) to reduce heart rate and improve image quality by increasing the relative time resolution during CCTA [1, 2]. In fact, many clinical and other types of studies of CCTA have reported the administration of β-blockers to lower heart rate for CCTA [3, 4].

One recent study reported high diagnostic capability with the assistance of the latest devices that shorten the imaging time and improve time resolution, without the use of β-blockers [5]. However, those results were obtained using only a specific model such as dual-source CT in an updated facility, and thus CT equipment commonly used in clinical practice still require the use of β-blockers to lower heart rate during CCTA. Furthermore, it is essential to lower the heart rate to reduce exposure volume [6, 7] as many techniques to reduce the volume of exposure to radiation are applicable only at low heart rates.

Injectable or oral β-blockers, which not only take more than 1 h to become effective but also have long half-lives [2.3 h for injection (propranolol), and 2.8 (metoprolol) to 3.9 h (propranolol) for tablets], thus constraining patients for a longer time, were widely used in previous studies. Therefore, short-acting β-blockers have been demanded in order to achieve safer and more efficient inspection. The pharmacokinetic profile of landiolol hydrochloride shows high β_1-selectivity as well as a very short half-life (3.97 min) [8]. Landiolol hydrochloride has been a useful agent for improving the image quality of CCTA by 64- and 320-slice multi-detector CT (MDCT) as it was confirmed to reduce heart rate significantly and rapidly after intravenous injection [9–11]. Although there are some studies in which the efficacy, safety, or usefulness of β-blockers has been explored [11, 12], no study has examined the usefulness and safety of short-acting β-blockers at an approved dosage and with approved administration in CCTA by 16-slice MDCT.

Nowadays, 64-slice CT or newer CT equipment with more slices have the most advanced functions. However, due to the cost of 64-slice CT, most small- and medium-sized hospitals still have 16-slice CT. Sixteen-row CT is less expensive than the newer CTs and is still widely used in Japan. In addition, new low-dose algorithms for the reduction of radiation exposure are also available in CCTA with 16-slice CT, and the X-ray exposure dose of 16-slice MDCT is less than that of the 64-slice MDCT [13, 14]. It is possible to obtain an appropriate coronary image by 16-slice MDCT [15–22] if the patient's heart rate during CCTA is properly controlled.

In the present study, the usefulness and safety of the short-acting β_1-receptor blocker landiolol hydrochloride (ONO-1101) 0.125 mg/kg for CCTA were assessed using 16-slice CT.

2 Methods

2.1 Study Population

Prior to CCTA, Japanese subjects aged 20 years and older who were suspected of having ischemic cardiac disease were selected based on symptoms recorded by a physician, physical examination, standard 12-lead ECG, chest X-ray, or echocardiography findings. The patients included in the study were those who (1) presented with stable angina syndromes and were referred for clinically indicated CCTA; and (2) had a heart rate of 70–90 beats/min before undergoing CT screening and immediately before administration of a nitrate vasodilator drug.

Patients were excluded from the present study if they had a cardiac pacemaker or defibrillator or both implanted; had undergone coronary-artery bypass surgery; had systolic blood pressure less than 110 mmHg before CCTA; had atrial fibrillation or extrasystoles at imaging; were pregnant, lactating, or possibly pregnant or desiring to become pregnant during the study period; required dialysis treatment; had clinically renal abnormalities defined as serum creatinine >1.5 mg/dL; or the use of β-blockers or non-ionic contrast media was contraindicated. The concomitant use of the following drugs was prohibited: non-dihydropyridine calcium antagonists, antiarrhythmic agents, sympathomimetic agents, and biguanide antidiabetic agents. However, the concomitant use of β-blockers or dihydropyridine calcium antagonists for conditions such as hypertension or angina was allowed.

The appropriateness of the study was reviewed and accepted by the Institutional Review Board at each study center before initiating the study. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki, and in compliance with the Pharmaceutical Affairs Law and the Ordinance on Standards for Implementation of Clinical Studies on Drugs (Ministry of Health and Welfare Ordinance No. 28) in Japan. Prior to the study, written informed consent was obtained from all patients upon confirming that they had understood the details of the study.

2.2 Study Design

The present study was a multicenter open-label study, which was conducted at nine study centers in Japan. The eligible subjects received landiolol hydrochloride (0.125 mg/kg) before CCTA. The landiolol hydrochloride dose selection was based on the previous phase II trials in which the efficacy and safety of the drug were examined [9, 10]. In addition, the dose of 0.125 mg/kg was selected in a phase III, double-blind trial [11]. As shown in Fig. 1, the subjects received the study drug as a bolus injection over 1 min after receiving a nitrate drug (nitroglycerin 0.3 mL was administered under the tongue), and underwent CCTA 4–7 min after administration of the study drug. The study period was between August 2009 and February 2010.

2.3 Endpoints

The primary endpoint was the diagnosable proportion (proportion of subjects whose coronary stenosis was diagnosable in reconstructed images). A higher diagnosable proportion expressed as a score can be achieved by improving the image quality. The diagnosable proportion has been reported to be improved at a heart rate not higher than 65 beats/min. Therefore, we investigated the relationship between the diagnosable proportion and heart rate in order to confirm the image quality-improving effect of administration of landiolol hydrochloride. The secondary endpoints were the degree and duration of the drug effect on heart rate and blood pressure, percutaneous oxygen saturation (SpO_2), ECG parameters, and adverse events. Heart rate (Holter ECG), blood pressure, and SpO_2 were monitored before initiation of the study (baseline: measured on the day of CCTA), before undergoing CT screening, immediately before administration of the nitrate drug, immediately before administration of the study drug, every minute between 0 and 10 min after completion of administration of the study drug, and at 15 and 30 min after completion of administration of the study drug. Additionally, 12-lead ECG and laboratory values were assessed before initiation of the study (baseline) and within 3 days after completion of administration of the study drug. Adverse events were followed from the initiation of study drug administration until the end of the monitoring period.

2.4 Coronary Computed Tomography Angiography

2.4.1 Image Acquisition

CCTA was performed between 4 and 7 min after completion of study drug administration. The reason for this timing of CCTA is that heart rate was reported to be the

Fig. 1 Time flow of study drug administration. The study drug was administered over 1 min, 5 or more min after nitrate drug administration. *CCTA* coronary computed tomography angiography, *CT* computed tomography
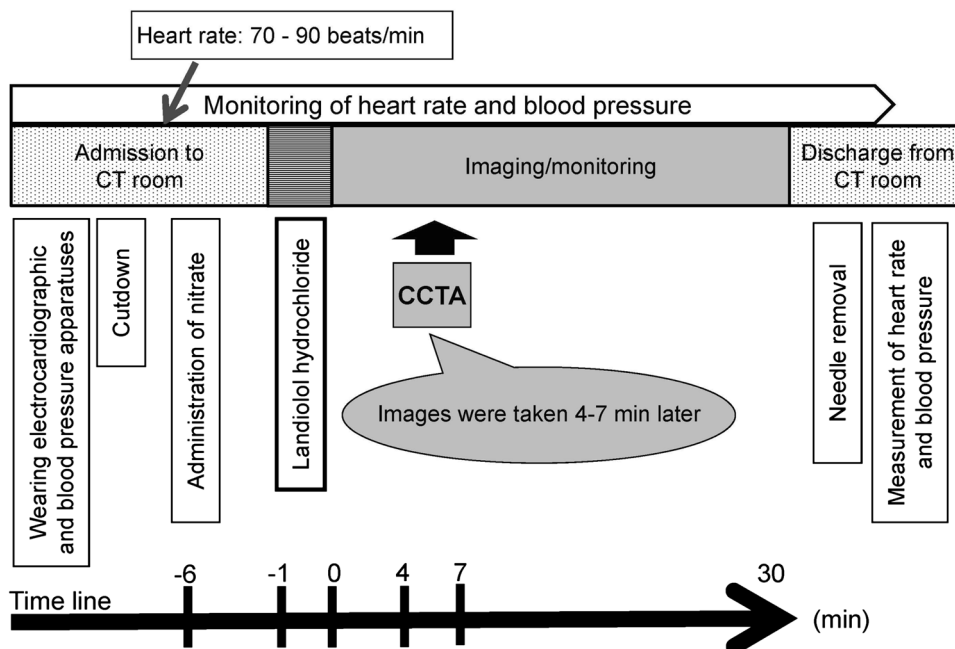
lowest between 4 and 7 min after intravenous administration of landiolol hydrochloride [8]. The CT equipment used were SOMATOM Sensation 16 (Siemens), SOMATOM Sensation Cardiac 16 (Siemens), Aquilion® 16 (Toshiba Medical Systems Co.), LightSpeed Ultra 16 (GE Medical Systems, Inc.), and LightSpeed Pro 16 (GE Medical Systems, Inc.). Table 1 shows the imaging conditions for each type of CT equipment. The rotation speed of the X-ray tube was set to the maximum for each type of equipment. Iopamidol (370 mgI/mL), a non-ionic contrast medium, was rapidly injected intravenously at 3–4.5 mL/s using a 2-channel injector followed by infusion of 20–30 mL saline.

2.4.2 Image Reconstruction

Image reconstruction followed the retrospective ECG-gated reconstruction method in each study center, with a slice thickness for reconstruction of 0.5–0.75 mm [0.75 mm for Siemens (16-slice), 0.5 mm for Toshiba (16), and 0.625 mm for GE (16)]. Image reconstructions for each image from subjects were performed with two conditions: one was at the optimal conditions for each study center and at mid-diastole (70 % of the R–R interval), and the other was the primary endpoint, evaluated by using the reconstruction images at mid-diastole.

2.4.3 Image Analysis

At the core laboratory, volume-rendering images, curved multi-planar reformation (MPR) images, interactive oblique MPR images, thin maximum intensity projection images, and cross-sectional images were prepared using the images reconstructed in the image analysis center of a third party. All images of each of 16 coronary segments based on the American Heart Association Classification were assessed and classified by the Central Coronary Visualization Judgment Committee, consisting of three independent radiodiagnostic specialists, as the image quality score: Score 1—motion artifact(s) present and impossible to diagnose; Score 2—motion artifact(s) present but diagnosable; and Score 3—no motion artifact and diagnosable. The image quality score was analyzed per subject, per

coronary vessel (total of four vessels: right coronary artery, left main coronary artery, left anterior descending, and left circumflex) and per coronary segment. The validity of this assessment (comparison with coronary angiographic findings) has already been confirmed by our phase II study [10].

Preparation of images as well as assessment of the diagnosable proportion were performed using a workstation Aquarius NET Server (Client PC networked with Aquarius NET Server) of the same model.

2.4.4 Statistical Analysis

The analysis of efficacy and safety was based on the full analysis set (FAS). The changes in the heart rate, blood pressure, and SpO_2 were examined by t test. A p value of <0.05 was considered statistically significant.

3 Results

A total of 39 subjects were enrolled and all subjects in this study received the study drug. During the study period, two subject discontinued the study (due to exclusion criteria violation and failure of CT equipment). The FAS for the efficacy and safety analyses was thus composed of 39 subjects as planned. One subject who did not meet eligibility criteria was excluded from the per-protocol set. The analysis set for image evaluation of the mid-diastole images was composed of 25 subjects. The analysis set for image evaluation of an optimal image was composed of 26 subjects (Fig. 2). The radiation dose for the CCTA was 9.03 ± 1.27 mSv for patients.

3.1 Baseline Characteristics

The background factors and CCTA conditions of the subjects enrolled in the present study are summarized in Table 2. Age [mean ± standard deviation (SD)] was 65.7 ± 10.3 years. Heart rate (mean ± SD) immediately before administration of the study drug was 77.1 ± 9.8 beats/min. Systolic blood pressure (mean ± SD) immediately before administration of the study drug was

Table 1 Imaging conditions for each type of computed tomography equipment

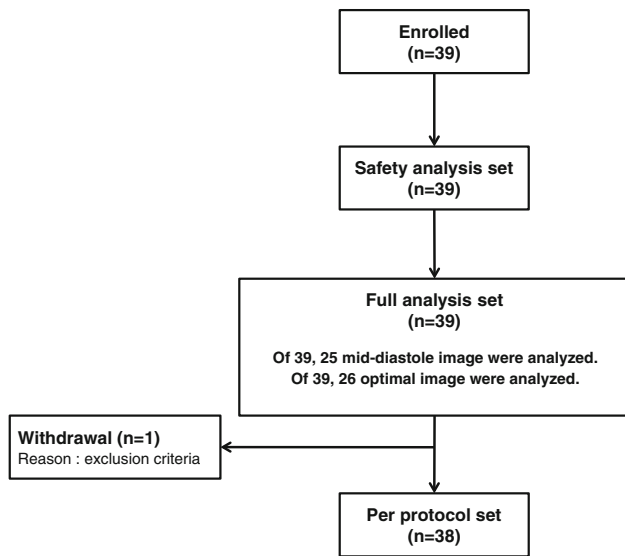| Imaging condition	Siemens (16-slice)	GE (16-slice)	Toshiba (16-slice)
Tube voltage (kv)	120	120	120
Tube current	770–850 mAs	400–750 mA	400–500 mA
Collimation (row × mm)	16 × 0.75	16 × 0.625	16 × 0.5
Rotation speed of X-ray tube (s/rotation)	0.375	0.4–0.5	0.4
Helical pitch	≤0.2	≤0.3	≤0.2
Field of view (mm)	200	200	200

Fig. 2 Flow diagram of subjects

128.7 ± 15.3 mmHg. The number of subjects by CT model was 16 for Siemens (16-slice), 14 for GE (16), and nine for Toshiba (16), respectively. The number (%) of subjects with concomitant use of oral β-blockers was three (7.7 %).

3.2 Heart Rate Evaluation

As shown in Table 3, heart rate at CCTA was 65.4 ± 8.0 beats/min, which was significantly lower than the value of 77.1 ± 9.8 beats/min before administration of the study drug (paired t test: $p < 0.0001$). The heart rate-lowering rate, defined as percent change from the baseline to CCTA, was −14.46 ± 8.4 % and the reduction rate showed statistical significance (paired t test: $p < 0.0001$) as did the mean heart rate at CTTA. The heart rate then rapidly recovered toward the baseline value at approximately 6 min after completion of the study drug administration (Fig. 3).

3.3 Blood Pressure Evaluation

As shown in Fig. 4, mean systolic blood pressure was not significantly lower than the value of 128.7 ± 15.3 mmHg before administration of the study drug (paired t test: $p = 0.6254$).

3.4 Percutaneous Oxygen Saturation Evaluation

Mean SpO_2 at 30 min after administration of the study drug was 97.9 ± 2.1 %, which was not significantly lower than the value of 97.3 ± 2.2 % before administration of the study drug.

Table 2 Baseline patient characteristics and coronary computed tomography angiography conditions

Parameter	Subjects
Patient characteristics	
No. of patients	39
Sex (male/female) [n (%)]	21/18 (53.8/46.2)
Age (years) [mean ± SD]	65.7 ± 10.3
Height (cm) [mean ± SD]	159.81 ± 9.61
Weight (kg) [mean ± SD]	61.952 ± 14.565
Subjects with angina symptoms [n (%)]	37 (94.9)
Heart rate (beats/min) [mean ± SD]	77.1 ± 9.8
Systolic blood pressure (mmHg) [mean ± SD]	128.7 ± 15.3
Diastolic blood pressure (mmHg) [mean ± SD]	71.1 ± 9.6
SpO_2 (%) [mean ± SD]	97.3 ± 2.2
Concomitant use with oral β-blocker	3 (7.7)
CCTA conditions	
CT equipment [n (%)]	
Siemens (16-slice)	16 (41.0)
GE (16-slice)	14 (35.9)
Toshiba (16-slice)	9 (23.1)
Time from completion of study drug administration to initiation of imaging (s) [mean ± SD]	315.7 ± 59.5
Scanning time (s) [mean ± SD]	21.7 ± 4.3
Number of subjects by administration speed of contrast medium [n (%)]	
<3.5 mL/s	28 (73.7)
3.5–4.0 mL/s	9 (23.7)
>4.0 mL/s	1 (2.6)
No data	1
Total dose of contrast medium and saline (mL) [mean ± SD]	120.4 ± 10.8

CCTA coronary computed tomography angiography, *CT* computed tomography, *SD* standard deviation, *SpO₂* percutaneous oxygen saturation

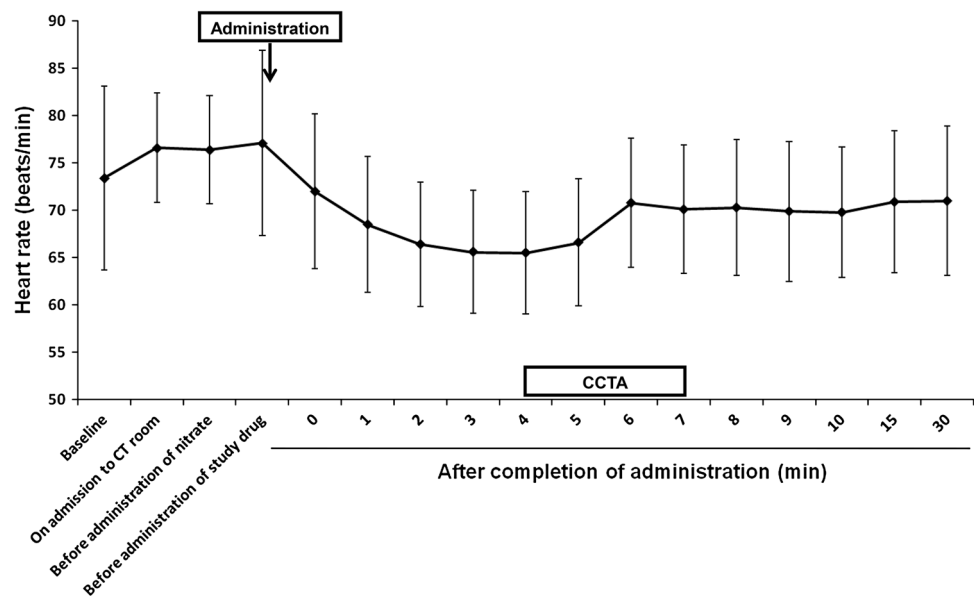## 3.5 Image Evaluation

3.5.1 Image Quality Score

As shown in Table 4, an image quality score of 2 or 3 for the reconstruction images at mid-diastole in the analysis by subject was observed in 56.0 % (14/25 subjects; 95 % CI 36.5–75.5). A score of 2 or 3 for the reconstruction images at mid-diastole in the analysis by coronary vessel was observed in 84.2 % (80/95 vessels; 95 % CI 76.9–91.5). A score of 2 or 3 for the reconstruction images at mid-diastole in the analysis by coronary segment was observed in 92.3 % (264/286 segments; 95 % CI 89.2–95.4).

An image quality score of 2 or 3 for the optimal reconstruction images in the analysis by subject was observed in 65.4 % (17/26 subjects). A score of 2 or 3 for

Table 3 Changes of heart rate and blood pressure at coronary computed tomography angiography

Parameter	Evaluation time point	Value
Heart rate (beats/min)	Before administration	77.1 ± 9.8
	At CCTA	65.4 ± 8.0
	Change rate (%)	−14.46 ± 8.4
Systolic blood pressure (mmHg)	Before administration	128.7 ± 15.3
	At CCTA	130 ± 21.1
	Change rate (%)	0.41 ± 8.12

Data are given as mean ± standard deviation

CCTA coronary computed tomography angiography

Fig. 3 Mean ± standard deviation changes in heart rate. Rotation speed of the X-ray tube was set at the maximum speed for each type of computed tomography equipment. *CCTA* coronary computed tomography angiography, *CT* computed tomography

the optimal reconstruction images in the analysis by coronary vessel was observed in 90.9 % (90/99 vessels). A score of 2 or 3 for the optimal reconstruction images in the analysis by coronary segment was observed in 96.3 % (286/297 segments).

In subgroup analysis by CT model, the proportion of subjects with image quality scores of 2 and 3 for the reconstruction images at mid-diastole was 50.0 % for Siemens (16-slice), 62.5 % for GE (16), and 57.1 % for Toshiba (16). The scores in the analysis for each CT model (Siemens, GE, and Toshiba) by coronary vessel and segment were 79.5, 86.7, and 88.5 % (by coronary vessel), and 88.4, 95.7, and 95.2 % (by coronary segment), respectively. These results show that landiolol is useful for imaging by any of the 16-slice MDCT models tested.

### 3.5.2 Relationship Between Diagnosable Proportion and Heart Rate

As shown in Fig. 5(a, images at mid-diastole; b, images at optimal conditions), although the diagnosable proportion of the reconstruction images at mid-diastole was only 42.9 % (at heart rate 65–69 beats/min) and the numbers of subjects

analyzed in each heart rate range were limited, the diagnosable proportion increased to 80.0 % (at heart rate 60–64 beats/min), 71.4 % (at heart rate 55–59 beats/min), and 100.0 % (at heart rate ≤54 beats/min), showing a positive correlation between the diagnosable proportion for the reconstruction images at mid-diastole and heart rate at CCTA by 16-slice MDCT (Fig. 5a). Regarding the optimal reconstruction images, the diagnosable proportion was only 62.5 % (at heart rate 65–69 beats/min) and the numbers of subjects analyzed were also limited (Fig. 5b). However, the diagnosable proportion increased to 80.0 % (at heart rate 60–64 beats/min), 85.7 % (at heart rate 55–59 beats/min), and 100.0 % (at heart rate ≤54 beats/min), showing a positive correlation between the diagnosable proportion for the reconstruction images at optimal conditions and heart rate at CCTA by 16-slice MDCT.

3.6 Safety and Tolerability

No subject died and no adverse reaction that required termination of study drug administration occurred during the study period.

Fig. 4 Mean ± standard deviation change in blood pressure. *CCTA* coronary computed tomography angiography, *CT* computed tomography, *DBP* diastolic blood pressure, *SBP* systolic blood pressure
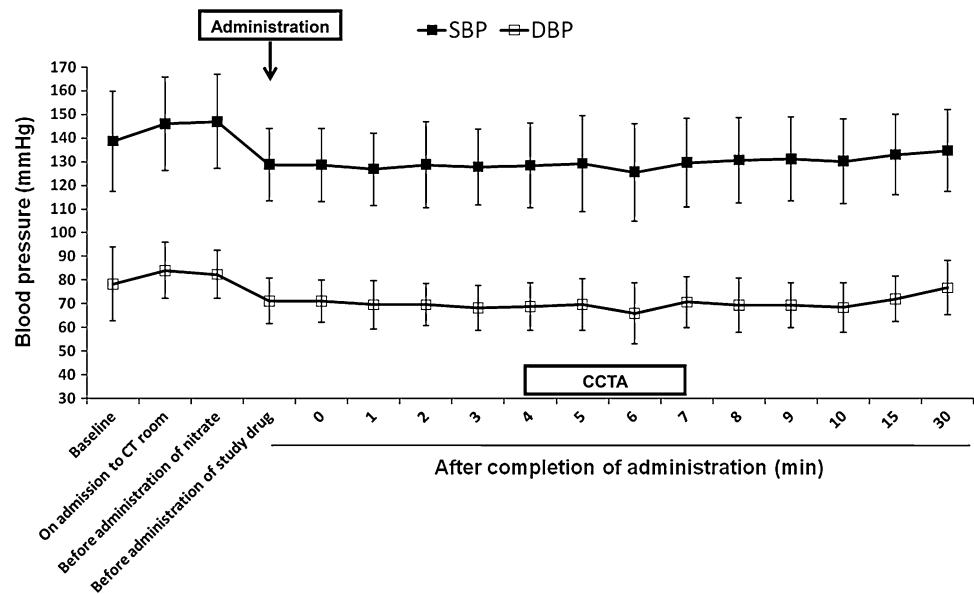
4 Discussion

In the present study, injection of the study drug was found to be effective to rapidly lower the heart rate soon after administration. The study drug, with a half-life of only 4 min, did not have a prolonged β-blocking effect after CCTA and lowered the heart rate only during CCTA (Fig. 3); therefore, hemodynamics do not need to be monitored for a long period after CCTA. In fact, in clinical practice using oral agents, patients must attend the hospital to take a β-blocking agent 1–2 h before initiation of CCTA and to monitor their heart rate to determine whether it meets the conditions for CCTA. This means it takes several hours before starting CCTA. In the case of this study drug, in contrast, administration is possible immediately before CCTA, allowing early completion of imaging. The results from the present study confirmed that this drug can be administered to patients just before CCTA, in contrast to oral agents requiring administration 1–2 h before CCTA. Thus, this drug appears to increase the efficiency of CCTA.

On the other hand, while bradyarrhythmia and hypotension induced by the β₁-blocking effect and broncho-constriction and peripheral circulatory disorder induced by the β₂-blocking effect are known adverse reactions of β-blockers, the primary adverse reactions to the study drug are likely to be bradyarrhythmia and hypotension because of the high selectivity of this drug for β₁-receptors (β₁/β₂: 251/1) [23, 24]. In the present study, no subject developed bradyarrhythmia and hypotension. Furthermore, this drug was shown to lower the heart rate only during CCTA (for approximately 30 min) and not to have a prolonged effect after the completion of CCTA, confirming its safety.

Meijboom et al. [25] and Marano et al. [26] confirmed the high diagnostic performance of CCTA in multivendor, multicenter clinical studies using other CT models. In the present study using 16-slice CTs from Siemens, Toshiba, and GE, which are widely used in Japan, CCTA was performed only in subjects with a pre-CT heart rate as high as 70–90 beats/min, confirming the efficacy and safety of injection of the short-acting β₁-receptor blocker landiolol hydrochloride. Consequently, the improvement in the diagnosable proportion as a result of this drug was considered not to be affected by the CT equipment model and concomitant use of β-blockers and dihydropyridine calcium antagonists.

In the present study, the median heart rate during CCTA was 64.5, and the proportion of the patients scanned with a heat rate under 65 beats/min was 50.0 % (17/34). With regard to the proportion of patients with a heart rate <65 beats/min, this can be attributed to the high heart rate population targeted for the current study and relatively long breath-holding during CCTA with 16-slice CT. In addition, only 65.4 % of patients with a high heart rate had good-quality images as a result of administration of the study drug. This seems to be caused by the high heart rate at baseline and long breath holding required during CCTA with 16-slice CT.

There have been many reports that the diagnosable proportion at CCTA by 16-slice MDCT is improved at a heart rate of 65 beats/min [15–21]. Therefore, efforts have been devoted to control the heart rate at not higher than 65 beats/min. However, this study demonstrated that approximately one-fifth of the subjects were affected by motion artifacts at a heart rate of under 60–64 beats/min, suggesting that a further reduction of heart rate is necessary to achieve sufficient image quality.

On the other hand, the relationship between image quality and heart rate in past clinical trials of this drug are

Table 4 Distribution of image quality score

Analysis unit	Image quality score	Type of the reconstructed images	
		Reconstruction images at mid-diastole	Optimal reconstruction images
By subject [n (%)]	3	0 (0.0)	0 (0.0)
	2	14 (56.0)	17 (65.4)
	1	11 (44.0)	9 (34.6)
	Total	25	26
	≥2	14 (56.0)	17 (65.4)
By coronary vessel [n (%)]	3	3 (3.2)	6 (6.1)
	2	77 (81.1)	84 (84.8)
	1	15 (15.8)	9 (9.1)
	Total	95	99
	≥2	80 (84.2)	90 (90.9)
By coronary segment [n (%)]	3	6 (2.1)	9 (3.0)
	2	258 (90.2)	277 (93.3)
	1	22 (7.7)	11 (3.7)
	Total	286	297
	≥2	264 (92.3)	286 (96.3)

Fig. 5 Relationship between diagnosable proportion and heart rate. There was a positive correlation between the diagnosable proportion and heart rate. **a** images at mid-diastole, **b** images at optimal conditions
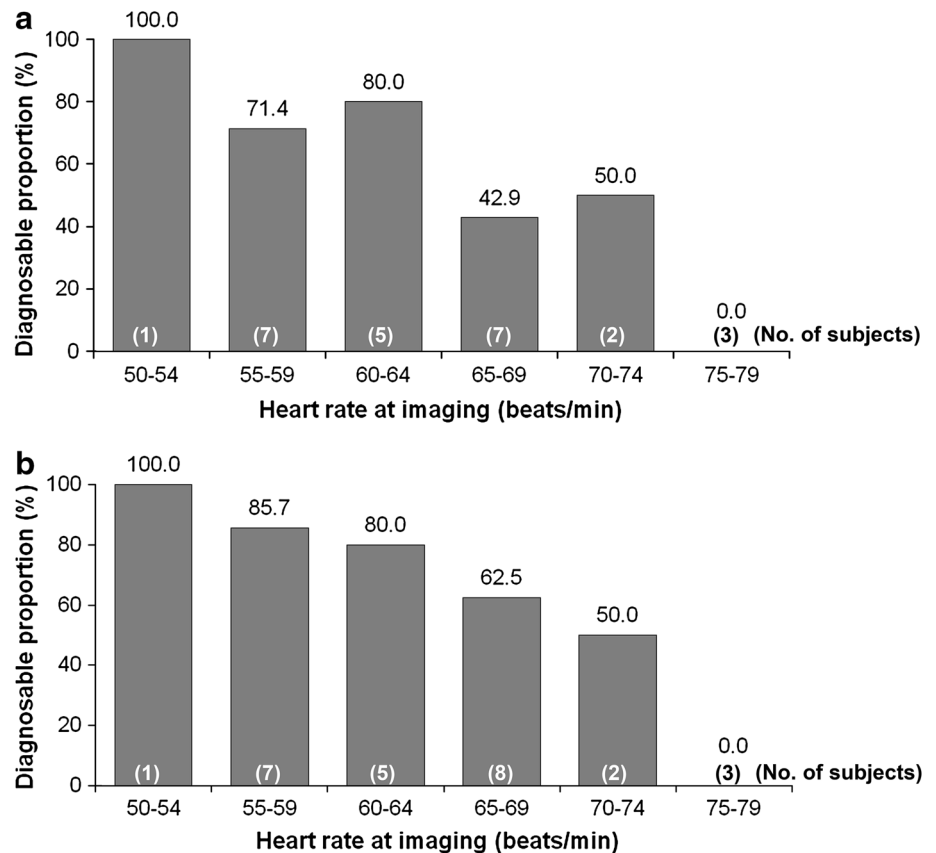
shown in Table 5. Time resolution of CT equipment depends on the rotation speed of the X-ray tube and detector. The main factor in motion artifact is an insufficient time resolution. Actually, when the patient's heart rate was properly controlled during CCTA, the diagnostic accuracy of 16-slice MDCT was as excellent as that of 64- or 320-row MDCT (Table 5).

In summary, landiolol hydrochloride was suggested to be useful as a β-blocking agent in order to improve the diagnosable proportion at CCTA by 16-slice MDCT

Table 5 The relationship between image quality and heart rate in past clinical trials of landiolol hydrochloride

Author	Type of MDCT (row)	Rotation speed of X-ray tube (s/rotation)	Before administration of oral β-blockers	Dose of landiolol (mg/kg)	Heart rate during CCTA* (bpm)	The diagnosable proportion (number of vessels, subjects or segments)					
						By subject		By coronary vessel		By coronary segment	
						Reconstruction image at mid-diastole	Optimal reconstruction image	Reconstruction image at mid-diastole	Optimal reconstruction image	Reconstruction image at mid-diastole	Optimal reconstruction image
This study	16	0.375–0.5	Yes	0.125	65.4 ± 8.0	56.0 % (14/25)	65.4 % (17/26)	84.2 % (80/95)	90.9 % (90/99)	92.3 % (264/286)	96.3 % (286/297)
Hirano et al. [9]	64	0.33	No	0.125	63.9 ± 7.8	None	61.5 % (16/26)	None	82.2 % (83/101)	None	93.9 % (290/309)
Jinzaki et al. [10]	64	0.33	No	0.125	62.6 ± 7.8	None	77.4 % (41/53)	None	89.4 % (168/188)	None	94.2 % (517/549)
Hirano et al. [11]	64/320	0.33–0.42	Yes	0.125	62.6 ± 8.5	68.2 % (75/110)	81.4 % (96/118)	87.8 % (360/410)	94.3 % (413/438)	92.9 % (1,169/1,259)	97.9 % (1,326/1,354)

bpm beats per min, *CCTA* coronary computed tomography angiography, *MDCT* multi-detector computed tomography

* mean ± standard deviation

because it decreased the effect of motion artifact induced by heart beats at CCTA and did not exhibit a prolonged β-blocking effect after the examination. Furthermore, administration of landiolol hydrochloride showed a positive correlation between the image quality score and heart rate.

4.1 Study Limitations

In the present study, we did not compare landiolol hydrochloride with placebo. We also investigated the usefulness and safety of landiolol in a small population ($n = 39$), despite a huge number of suspected ischemic heart disease cases in Japan. Calcium scoring was not employed as an inclusion or exclusion criterion in the present study, which excluded subjects whose heart rate was higher than 90 beats/min before CCTA (regardless of the heart rate immediately before administration of the study drug) and subjects expected to develop arrhythmia during CCTA.

5 Conclusions

Landiolol hydrochloride was confirmed to lower heart rate significantly and rapidly after intravenous injection, suggesting that it is a safe and useful agent for improving the image quality of CCTA by 16-slice MDCT.

Appendix: Principal Investigators

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