Feasibility of Intravenous Administration of Landiolol Hydrochloride for Multislice Computed Tomography Coronary Angiography

--- Initial Experience ---

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Background  The feasibility of using landiolol hydrochloride in multislice computed tomography (MSCT) coronary angiography (CAG) was investigated in the present study.

Methods and Results  Landiolol hydrochloride was continuously administered intravenously to 145 patients before starting MSCT CAG. Hemodynamic changes [blood pressure (BP), heart rate (HR)], adverse effects, image quality using a 5-point scale, and accuracy of detecting significant stenoses (≥50% reduction in lumen diameter) were evaluated. HR was significantly reduced during injection, and quickly recovered after cessation of administration, of landiolol hydrochloride. Neither significant changes in BP nor adverse effects occurred. Among visible segments, 1,869 (94%) displayed an excellent (83%) or good (11%) image quality. Diagnostic accuracy was evaluated in 39 of 145 patients who underwent invasive CAG within 3 weeks after MSCT. The sensitivity, specificity, positive predictive value, and negative predictive value of MSCT CAG for detection of significant stenoses in assessable segments were excellent (per artery: 94%, 98%, 92%, and 100%; per segment: 92%, 98%, 94%, and 96%, respectively).

Conclusions  Intravenous administration of landiolol hydrochloride reduces HR without a significant reduction in BP, which enables favorable image quality and diagnostic accuracy without adverse effects, making this agent feasible as a premedication for MSCT CAG. (*Circ J 2008; 72: 1814–1820)

Key Words:  Image quality; Landiolol hydrochloride; Multislice computed tomography coronary angiography; Premedication

Multislice computed tomography (MSCT) coronary angiography (CAG) is emerging as a powerful noninvasive imaging strategy for the evaluation of atherosclerosis in patients with known or suspected coronary artery disease (CAD).1–10 MSCT CAG not only assesses the degree of stenosis in the coronary lumen, but also provides direct information regarding the nonobstructive atherosclerotic plaque burden and plaque morphology within the vessel wall.11,12

Despite technological advances, MSCT CAG has important limitations, such as motion artifacts resulting from a high heart rate (HR).13,14 Residual motion artifacts hamper attainment of excellent image quality, leading to a reduction in diagnostic accuracy in detecting significant CAD. In particular, imaging of patients with a high HR often renders the coronary segments unassessable and coronary artery images are frequently affected by motion artifacts.15 The β-blockers are often given orally before MSCT CAG to reduce HR and stabilize image quality. Sixteen-slice MSCT CAG with β-blocker premedication produces images of diagnostically acceptable quality, and the number of unassessable coronary segments because of motion artifacts is markedly reduced.16 To ensure an optimal dose for reducing HR for image acquisition, intravenous administration of β-blockers is reasonable because it allows better titration than oral administration; however, the effectiveness of intravenous β-blocker administration has not been widely established.

In this study we investigated the feasibility of intravenous injection of landiolol hydrochloride (Onoact, Ono Pharmaceutical Co, Osaka, Japan), a recently developed ultrashort-acting β1-selective agent, for MSCT CAG.

Methods

Population  The study included 145 patients with known or suspected CAD (chest pain complaints, elevated risk profile, or abnormal test results). All patients underwent MSCT CAG on admission to hospital. Inclusion criteria were typical chest pain with a stable condition, positive stress ECG tests, resting ECG abnormalities (suspected ischemic heart disease), and multiple coronary risk factors regardless of type (ie, typical or atypical) of chest pain (at least 2 risk factors were required).
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Factors among hypertension, hyperlipidemia, diabetes, and smoking). Patients with suspected progression of CAD (prior myocardial infarction or stable angina pectoris) were also included in the study. Patients were excluded if they had any of the following: an unstable clinical condition (presenting with an acute coronary syndrome); renal dysfunction (serum creatinine level >1.5 mg/dl [133 μmol/L]); pregnancy; thyroid disorder; and inability to follow breath-holding commands. Further exclusion criteria were an irregular HR, bradycardia ≤55 beats/min, contraindication for β-blockers (e.g., bronchial asthma, chronic obstructive pulmonary disease, advanced atrioventricular block), or a history of previous allergy to iodine-containing contrast medium. Patients with previous myocardial infarction or those with a coronary stent were included, but patients who had undergone coronary artery bypass graft surgery were excluded.

The institutional review board approved this study in May 2007. The aim of the study was explained to all patients and written informed consent was given.

Landiolol Hydrochloride

Landiolol hydrochloride, [4R-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 3-[4-[(2S)-2-hydroxy-3-[2-(morpholine-4-carbonylamino)ethylamino]propoxy]phenyl] propanoate hydrochloride, a new β1-selective agent with a pharmacological resemblance to esmolol, was recently synthesized by Ono Pharmaceutical Co. The chemical structure is presented in Fig 1. In the present study it was continuously injected intravenously using an infusion pump from 15 min before starting MSCT CAG. The starting dose was 0.02 mg·kg⁻¹·min⁻¹ and was increased until HR ≤55 beats/min. Injection was discontinued immediately after the completion of MSCT scanning. A time-line diagram of the study protocol is shown in Fig 2.

**Protocol**

![Protocol Diagram](image)

**MSCT CAG Data Acquisition and Interpretation**

MSCT CAG data were acquired using a SOMATOM 16 CT scanner (Siemens Medical Solutions, Forchheim, Germany) with landiolol hydrochloride administration. Initial scans to determine the precise position of the heart were performed without contrast medium. Patients received 0.3 mg of nitroglycerin immediately prior to MSCT scanning, after which 75 ml of a nonionic contrast medium (Optiray 320, Tyco Healthcare Tokyo, Japan) was injected intravenously at a rate of 5 ml/s, followed by a 50-ml saline chaser. Computed tomography with contrast medium started at the aortic root cranial to the coronary ostia and stopped at the diaphragm, taking care to include all cardiac structures. Scan parameters were as follows: detector col-
limation, 16×0.75 mm; gantry rotation time, 400 ms; table feed, 3 mm/rotation; tube voltage, 120 kV; and tube current, 400–450 mA. Prospectively triggered X-ray tube current modulation was applied for patients with HR <60 beats/min and showing no arrhythmia during a monitoring period of approximately 1 min. This feature reduces the radiation output of the X-ray tube during the less important systolic phase, thereby decreasing the total radiation dose by 40–50%.

To obtain nearly motion-free image quality, axial slices were reconstructed within the mid- to end-diastolic phase. These datasets were reconstructed, with reconstruction windows starting at 350, 400, and 450 ms before the next R wave. All datasets were screened by axial scrolling to check for the presence of motion artifacts.Datasets with the fewest artifacts in a single coronary vessel were selected and postprocessed on a subconsole linked to the CT scanner. Depending on the coronary morphology and dataset quality, 3 postprocessing techniques were applied to assess the coronary arteries: (1) maximum intensity projection, (2) curved multiplanar reconstruction and (3) volume rendering. Image quality was evaluated on a per-segment basis by 2 experienced observers who were unaware of the data obtained by conventional CAG, and was classified using a 5-point grading scale as previously described:17 excellent (no motion artifact); good (minor motion artifact); moderate (substantial motion artifact but possible to assess lumen); heavily calcified (vessel lumen obscured by calcification); and blurred (not possible to assess lumen). MSCT CAG data sets were evaluated for the presence of significant coronary artery stenosis according to the AHA classification.18 Stenosis with a diameter ≥50% of normal were considered significant. Lesions in which a coronary stent had been implanted were excluded from analysis.

Conventional CAG
Conventional CAG was performed within 3 weeks after MSCT CAG according to standard procedures. Angiograms were analyzed using quantitative CAG software (CAAS; Pie Medical, Maastricht, The Netherlands) by an experienced interventional cardiologist who was unaware of the clinical data, including the MCST CAG results. Coronary arteries were divided into 15 segments according to the AHA classification.18 Coronary lesions were evaluated on the basis of quantitative CAG, and significant stenosis was defined as a narrowing of the lumen diameter by ≥50%.

Monitoring of Adverse Effects of the β-Blocker and Contrast Medium

Hemodynamic changes [systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR] were evaluated before injection, during injection, and 15 min and 1 h after the cessation of injection of landiolol hydrochloride. Blood pressure (BP) and HR were monitored until sleep. BP, HR, and HR variability (difference between maximum and minimum HR for 1 min on a monitor ECG) were checked every minute after starting administration of landiolol until the CT scan was started. An intravenous drip of 500 ml of saline (0.9%) was administered to wash away the contrast medium. Potential adverse effects of landiolol hydrochloride, such as hypotension (including symptomatic orthostatic hypotension), a floating sensation, dizziness, serious bradyarrhythmia (complete atrioventricular block, sick sinus syndrome), and cardiogenic shock, were monitored for at least 6 h. Potential adverse effects of the contrast medium, such as allergic skin eruption, dyspnea, and allergic shock, were monitored for 24 h and adverse drug effects, BP, and HR were checked by nurses.

Statistical Analysis
Data are expressed as means ±SD. One-way ANOVA was performed followed by a post-hoc Bonferroni test to examine differences in the time course of changes in BP and HR. An unpaired t-test was used to examine the difference in HR variability before and during landiolol administration. Results from the 2 angiographic techniques were compared using a per-artery analysis (left anterior descending, left circumflex, right coronary, and left main arteries) and a per-segment analysis, with CAG serving as the reference gold standard. The diagnostic accuracy of MSCT CAG is expressed as the sensitivity, specificity, negative predictive value, and positive predictive value with reference to individual coronary segments. A p-value <.05 was considered statistically significant.

Results
Of 145 patients, 86 (59%) were men and the mean age was 63.4±8.2 years old. Thirty-nine (27%) patients had a history of heart disease (previous myocardial infarction, 5 patients; angina pectoris, 25 patients; congestive heart failure, 9 patients). Twenty-nine (20%) patients had a familial history of ischemic heart disease. Cardiovascular risk factors were distributed as follows: hypertension, 102 (70%) patients; hyperlipidemia, 83 (57%) patients; diabetes mellitus, 68 (47%) patients; and smoking, 55 (38%) patients. Thirty-two (22%) patients had typical angina symptoms. Patient characteristics are listed in Table 1.

The final dose of landiolol hydrochloride was 0.036±0.005 mg·kg⁻¹·min⁻¹. No significant changes in BP were observed, but gradual reduction of HR started approximately 5 min after the start of landiolol administration (Fig 3A). The mean SBP and DBP before injection were 135.2±18.7 mmHg and 73.4±11.4 mmHg, respectively, and these did not change significantly over the time course of the study (SBP: during injection, 135.2±18.3 mmHg; 15 min after cessation of injection, 130.9±19.1 mmHg; 1 h after cessation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics (n=145)</th>
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<tbody>
<tr>
<td>Gender (M/F)</td>
<td>86/59</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.4±8.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4±3.2</td>
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<tr>
<td>History of HD</td>
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<td>Myocardial infarction</td>
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</tr>
<tr>
<td>Angina pectoris</td>
<td>25</td>
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<tr>
<td>Congestive heart failure</td>
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<td>History of CVD</td>
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<tr>
<td>Familial history of IHD</td>
<td>29 (20%)</td>
</tr>
<tr>
<td>Familial history of CVD</td>
<td>30 (21%)</td>
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<tr>
<td>Risk factors</td>
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<tr>
<td>Hypertension</td>
<td>102 (70%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>83 (57%)</td>
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<td>Diabetes</td>
<td>68 (47%)</td>
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<td>Typical angina</td>
<td>32 (22%)</td>
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<tr>
<td>Atypical angina</td>
<td>38 (26%)</td>
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</tbody>
</table>

Data are expressed as means ±SD. BMI, body mass index; HD, heart disease; CVD, cerebrovascular disease; IHD, ischemic HD.
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of injection, 136.5±17.6 mmHg; before sleep, 134.8±16.2 mmHg; DBP: during injection, 72.4±11.1 mmHg; 15 min after cessation of injection, 70.2±12.2 mmHg; 1 h after cessation of injection, 73.0±10.6 mmHg; before sleep, 71.9±8.9 mmHg) (Fig 3B). The mean HR before injection of landiolol hydrochloride was 67.2±7.2 beats/min, and all patients achieved a target HR ≤55 beats/min at the start of the CT scan. The mean time to reach the target HR was 13.4±3.8 min. HR was significantly reduced during injection of landiolol hydrochloride (51.8±3.1 beats/min, p<0.0001), quickly recovered 15 min after cessation of injection (62.8±7.9 beats/min), and was maintained until sleep (1 h after cessation of injection, 66.0±7.5 beats/min; before sleep, 64.6±7.3 beats/min) (Fig 3B). HR variability was significantly reduced during CT acquisition compared with before administration of landiolol (4.1±1.8 vs 2.3±1.4 beats/min, p<0.0001).

No adverse effects from landiolol hydrochloride or contrast medium were reported during hospitalization. Two patients had a headache and 4 patients experienced facial flushing after nitroglycerin administration, but these symptoms improved within 30 min.

Fig 3. (A) Time course of changes in blood pressure (BP) and heart rate (HR) every minute after the start of injection of landiolol. There was no significant change in BP, but HR started to decrease approximately 5 min after injection. (B) Changes in BP and HR before injection, during injection, 15 min after cessation of injection, 1 h after cessation of injection, and before sleep. HR was significantly reduced during injection of landiolol (*p<0.0001 vs before injection, †p<0.0001 vs 15 min after cessation of injection, ‡p<0.0001 vs 1 h after cessation of injection, ¶p<0.0001 vs before sleep).

Fig 4. Visual diagnostic accuracy of multislice computed tomography (MSCT) coronary angiography (CAG) in segment-based (white bars) and artery-based (black bars) analysis. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.
Of 2,175 segments, 1,979 (91%) were visible. Image quality was graded as excellent in 1,652 (83%) segments, good in 217 (11%), moderate in 44 (2%), heavily calcified in 35 (2%) and blurred in 31 (2%).

Eighty (55%) patients had significant coronary stenoses. Of these patients, 39 (27%) who showed positive stress ECG tests, positive stress myocardial perfusion scintigraphy findings, or typical symptoms of angina underwent conventional CAG within 3 weeks after MSCT CAG. Among them, image quality was graded as excellent in 488 segments, good in 54, moderate in 11, heavily calcified in 22, and blurred in 10 segments. Ultimately, 553 segments considered as assessable and all available coronary segments were included in the evaluation regardless of size. For the presence of disease, 57 significant stenoses in 38 of 39 patients were detected correctly by MSCT CAG (sensitivity: 97%). Twenty-one patients had 1-vessel disease, 13 had 2-vessel disease, 4 had 3-vessel disease, and 1 patient had left main coronary stenosis with 2-vessel disease. Failure to detect a significant stenosis in the left anterior descending coronary artery by MSCT CAG occurred in only 1 patient. In the per-artery analysis, the sensitivity, specificity, positive predictive value, and negative predictive value of MSCT CAG for detection of significant stenosis in the assessable segments were 94%, 98%, 92%, and 100%, respectively, compared with conventional CAG (Fig 4).
the per-segment analysis, the corresponding values were 92%, 98%, 94%, and 96%, respectively (Fig 4).

Typical patients in whom significant CAD was detected correctly by MSCT CAG are presented in Figs 5A, B.

Discussion

Landiolol hydrochloride, a new \(\beta\)-selective agent that has a pharmacological resemblance to esmolol\(^{19,20}\) was used in this study for reducing HR. It has previously been demonstrated that landiolol hydrochloride has greater \(\beta\)-selectivity and a shorter elimination half-life (1/2) than esmolol\(^{21}\). Landiolol has the following unique characteristics: it is metabolized very quickly by serum pseudocholinesterase and carboxylesterase in the liver to an inactive metabolite with a short 1/2 of 4 min; renal clearance and hepatic clearance do not contribute to its pharmacokinetics, which indicates that it is titratable; it has very rapid onset and offset of action; no intrinsic sympathomimetic activity or significant membrane-stabilizing activity; and potential for suppressing tachyarrhythmias.\(^{21}\) Thus, the advantage of landiolol for clinical use is that it is very short-acting and highly selective for \(\beta\)-receptors, allowing easy titration and resulting in fewer side-effects, such as bronchial asthma or peripheral vasodilatation, than other longer acting \(\beta\)-adrenergic antagonists.

These characteristics make landiolol a promising new alternative to clinically available intravenous \(\beta\)-blockers, and its safety and effectiveness for urgent use in patients with tachyarrhythmia during the perioperative phase in the intensive care unit or operation room have been documented.\(^{22}\) Landiolol has the following unique characteristics: it is metabolized very quickly by serum pseudocholinesterase and carboxylesterase in the liver to an inactive metabolite with a short 1/2 of 4 min; renal clearance and hepatic clearance do not contribute to its pharmacokinetics, which indicates that it is titratable; it has very rapid onset and offset of action; no intrinsic sympathomimetic activity or significant membrane-stabilizing activity; and potential for suppressing tachyarrhythmias.\(^{21}\) Thus, the advantage of landiolol for clinical use is that it is very short-acting and highly selective for \(\beta\)-receptors, allowing easy titration and resulting in fewer side-effects, such as bronchial asthma or peripheral vasodilatation, than other longer acting \(\beta\)-adrenergic antagonists.

The characteristics make landiolol a promising new alternative to clinically available intravenous \(\beta\)-blockers, and its safety and effectiveness for urgent use in patients with tachyarrhythmia during the perioperative phase in the intensive care unit or operation room have been documented.\(^{22}\) However, there is no information regarding the effect of landiolol on hemodynamics in MSCT CAG. The current study indicated only a transient reduction in HR and no significant change in BP during or following administration of landiolol, suggesting that it may be useful in MSCT CAG. Moreover, our results demonstrated acceptable diagnostic accuracy, indicating that landiolol aids in assessment of CAD by MSCT CAG. Adequate reduction of HR is the most important manipulation for avoidance of motion artifacts and stabilization of image quality, and well-controlled reduction in HR has been reported not only to provide better image quality but also to minimize radiation exposure.\(^{23}\) HR variability also influences image quality in MSCT CAG\(^{24,25}\) and in the current study was significantly reduced during the CT scan. Therefore, our results indicate that continuous intravenous administration of landiolol is promising as a premedication for producing an appropriate HR for MSCT CAG without hemodynamic or physical adverse effects.

The diagnostic performance of 16-slice MSCT CAG in detecting significant coronary stenosis has been previously reported\(^{6,26}\) with the sensitivity, specificity, positive predictive value, and negative predictive value for a segment-based analysis in the ranges 73–95%, 82–93%, 59–80%, and 90–98%, respectively, compared with conventional CAG. In the present study, these parameters for detecting significant stenosis were comparable to previous reports, and we obtained a higher specificity and positive predictive value. However, our results should be interpreted with caution, because only selected patients undergoing invasive CAG for evaluation of significant coronary stenosis and assessable coronary segments were included. Diagnostic accuracy may be influenced by inclusion criteria and modalities of analysis\(^{6,26}\) and may change depending on the diameter of the vessel examined, its extent of calcification, poor opacification, and blending with veins. In this study, heavily calcified, stent-implanted, and bypass-graft (unassessable) lesions were excluded from analysis, although every assessable branch was included regardless of diameter.

It is possible that the better image quality obtained in this study was a consequence of the \(\beta\)-blocker being injected intravenously and combined with sublingual nitroglycerin rather than being used alone or administered orally. In addition, continuous intravenous injection of a \(\beta\)-blocker more readily enabled dose titration to achieve the target HR ≤55 beats/min in each patient. An inverse correlation between HR and image quality of MSCT CAG has been reported\(^{11,27}\) and our images may have had fewer motion artifacts because the mean HR was less than that in other studies. These factors may be additional reasons why better image quality and higher specificity and positive predictive value were obtained compared with previous studies.

The \(\beta\)-blockers may induce coronary spasm, and nitroglycerin, a widely used coronary vasodilator, may prevent \(\beta\)-blocker-induced coronary spasm. We used sublingual nitroglycerin to match standard practice for conventional CAG in most centers. To increase the number of visible segments and achieve diagnostic accuracy, the combined use of intravenous \(\beta\)-blocker injection with sublingual nitroglycerin appears to be reliable. We also note that to accomplish the aim of the study only inpatients were included. However, we believe that our study design can be extended to outpatients for whom MSCT CAG is planned, although it is advisable to monitor hemodynamic changes and adverse effects for at least a few hours for both inpatients and outpatients.

Study Limitations

First, the study was performed in only 145 patients and, in particular, diagnostic accuracy compared with conventional invasive CAG was evaluated in a highly selective group of 39 patients. Therefore, we cannot reach firm conclusions regarding the safety of landiolol or diagnostic accuracy using a patient-based analysis, and these issues warrant further investigation in a larger population. Second, in comparison with the recently introduced 64-slice MSCT scanner, a 16-slice scanner has reduced slices per gantry rotation and slower gantry speed, which translate into inferior spatial and temporal resolution. Moreover, the scanning time is longer, requiring an increased breath-holding time, and a reduced focus of contrast medium with greater enhancement of adjacent structures, requiring a higher dose of contrast media.\(^{28}\) Therefore, data obtained with 16-slice MSCT tend to be less sensitive and specific. Finally, it is unclear whether intravenous administration of a \(\beta\)-blocker is actually more feasible than oral administration for reducing HR in MSCT CAG because we did not compare patients receiving intravenous administration with those receiving oral administration.

Conclusions

Intravenous administration of the ultrashort-acting \(\beta\)-blocker, landiolol hydrochloride, produced an appropriate reduction in HR without a significant reduction in BP, resulting in favorable image quality and diagnostic accuracy without significant adverse effects. Therefore, we suggest that landiolol is a feasible premedication for MSCT CAG.
References


