Comparison of Contrast Media and Low-Molecular-Weight Dextran for Frequency-Domain Optical Coherence Tomography

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Background: Although an intracoronary frequency-domain optical coherence tomography (FD-OCT) system overcomes several limitations of the time-domain OCT (TD-OCT) system, the former requires injection of contrast media for image acquisition. The increased total amount of contrast media for FD-OCT image acquisition may lead to the impairment of renal function. The safety and usefulness of the non-occlusion method with low-molecular-weight dextran L (LMD-L) via a guiding catheter for TD-OCT image acquisition have been reported previously. The aim of the present study was to compare the image quality and quantitative measurements between contrast media and LMD-L for FD-OCT image acquisition in coronary stented lesions.

Methods and Results: Twenty-two patients with 25 coronary stented lesions were enrolled in this study. FD-OCT was performed with the continuous-flushing method via a guiding catheter. Both contrast media and LMD-L were infused at a rate of 4 ml/s by an autoinjector. With regard to image quality, the prevalence of clear image segments was comparable between contrast media and LMD-L (97.9% vs. 96.5%, P=0.90). Furthermore, excellent correlations were observed between both flushing solutions in terms of minimum lumen area, mean lumen area, and mean stent area. The total volumes of contrast media and of LMD-L needed for OCT image acquisition were similar.

Conclusions: FD-OCT image acquisition with LMD-L has the potential to reduce the total amount of contrast media without loss of image quality. (Circ J 2012; 76: 922–927)

Key Words: Contrast media; Intracoronary imaging; Low-molecular-weight dextran L; Optical coherence tomography

Intravascular optical coherence tomography (OCT), which is based on near-infrared light reflectivity, is a high-resolution imaging modality used in intracoronary assessment. OCT allows us to assess not only microstructural characterization of coronary plaques but also various abnormal findings after stent implantation including incomplete stent apposition, tissue protrusion, edge dissection, and thin neointimal formation following stent implantation, which are difficult to evaluate on intravascular ultrasound (IVUS). But OCT technology has several limitations, including signal attenuation by red blood cells. One experimental study has demonstrated that dextran improves OCT blood penetration. We previously reported the safety and usefulness of the non-occlusion method for OCT image acquisition with low-molecular-weight dextran L (LMD-L) via a guiding catheter. Furthermore, it has been reported that an intracoronary frequency-domain OCT (FD-OCT) system overcomes several limitations of the conventional time-domain OCT (TD-OCT) systems and has excellent reproducibility for consecutive pullbacks with contrast media in vivo. Meanwhile, the FD-OCT system requires injection of contrast media for image acquisition. The usage of contrast media for OCT image acquisition increases the total amount of contrast media and may lead to impairment of renal function. Therefore, there is considerable potential to reduce the risk of development of renal dysfunction if OCT images can be acquired with LMD-L in place of contrast media. The aim of the present study was to compare the image quality and quantitative measurements between contrast media and LMD-L for FD-OCT image acquisition in the assessment of coronary stented lesions.
Methods

Subjects
The subjects consisted of 22 ischemic heart disease patients with 25 chronic implanted coronary stents between October and December 2009. We excluded patients with New York Heart Association class III or IV heart failure, unstable hemodynamic status, and renal dysfunction (serum creatinine ≥1.5 mg/dl). The lesion-specific exclusion criteria were as follows: (1) stent diameter <2.5 mm; (2) stents located in the left main coronary artery; and (3) stents located in heavily calcified or highly tortuous vessels.

The protocol for this study was approved by the institutional ethics committee of Wakayama Medical University and we also obtained written informed consent from all patients before participation in this study.

Study Protocol
FD-OCT was performed in all patients using a 6-Fr Judkins-type catheter via the femoral approach after angiogram or angioplasty. All patients received an i.v. bolus injection of 5,000 IU heparin and intracoronary injection of 1.0-2.0 mg isosorbide dinitrate before the OCT procedure. In each patient, FD-OCT was performed with the continuous-flushing method using both contrast media iohexol (Omnipaque® 350 Injection; Daiichi Pharmaceutical, Tokyo, Japan) and a mixture of commercially available dextran 40 and lactated Ringer’s solution (Low Molecular Dextran L Injection®; Otsuka Pharmaceutical Factory, Tokushima, Japan) warmed at 37°C as the flushing solution via a guiding catheter, by the same doctors specializing in OCT, each of whom had performed TD-OCT using the non-occlusion method in more than 50 cases. The entire length of the target stent segment was completely observed using both contrast media and LMD-L. Beat-by-beat hemodynamic and electrocardiogram changes were recorded during injection of each flushing medium for image acquisition.

FD-OCT System and Catheter
The FD-OCT system (C7 system; LightLab Imaging, Westford, MA, USA) consists of an intravascular OCT catheter (RX ImageWire II; LightLab Imaging), an imaging engine, probe interface unit, and a computer console, which also contains the data acquisition board. The 2.7-Fr C7 catheter can be delivered as a mini-rail rapid exchange catheter over a 0.014-in (0.36 mm) coronary guidewire through a 6-Fr guiding catheter. After the C7 catheter was positioned so that its imaging lens was distal to the stent, contrast media and LMD-L were infused, respectively, at a rate of 4 ml/s by an autoinjector (Mark V; Medrad, PA, USA) under the pressure limit of 2.8 MPa. FD-OCT images were calibrated by adjusting the Z-offset before each pullback for image acquisition to obtain accurate measurements. All OCT images from the C7 system were obtained using an automatic pullback device traveling at a rate of 20 mm/s. The OCT
FD-OCT Analysis

All of the OCT frames in all of the pullbacks from FD-OCT (C7) systems were analyzed by 2 independent experienced observers (H.K. and K.K.) using the proprietary offline software (LightLab Imaging). The observers inspected each OCT pullback on a frame-by-frame basis along the length of the pullback images. Any discrepancies between the observers were resolved by a consensus reading.

The comparative parameter was the cumulative number of clear image segments (CIS) through the entire stent image, defined as those containing at least 1 clear image frame (CIF) within a 1-mm longitudinal segment, as shown in Figure 1. The CIF was defined as an OCT cross-sectional image frame in which the boundary between the lumen and the vessel wall was discernable along a continuous arc of at least 270° relative to the center of the lumen, as previously described.8 In terms of quantitative assessment, lumen area (LA) and stent area (SA) were measured at every 1-mm cross-section, respectively.

Measurement of Viscosity

Each flushing medium and a mixture of blood and each flushing medium (1:1) were warmed at 37°C and the viscosity was measured using a Cannon-Fenske Routine viscometer (Cannon® Instrument Company, PA, USA).

Table 1. Comparison of Image Quality

<table>
<thead>
<tr>
<th></th>
<th>Contrast</th>
<th>Dextran</th>
<th>P value</th>
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<tbody>
<tr>
<td>Total image analysis segment, n</td>
<td>525</td>
<td>538</td>
<td></td>
</tr>
<tr>
<td>Clear image segment, n (%)</td>
<td>514 (97.9)</td>
<td>519 (96.5)</td>
<td>0.90</td>
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</table>

Table 2. Stent Parameters (25 Stents in 22 Patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Patient age (years)</td>
<td>68±7</td>
</tr>
<tr>
<td>Male</td>
<td>16 (70)</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Stent diameter</td>
<td></td>
</tr>
<tr>
<td>2.5 mm</td>
<td>5 (20)</td>
</tr>
<tr>
<td>2.75 mm</td>
<td>1 (4)</td>
</tr>
<tr>
<td>3.0 mm</td>
<td>10 (40)</td>
</tr>
<tr>
<td>3.5 mm</td>
<td>5 (20)</td>
</tr>
<tr>
<td>4.0 mm</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>20±5</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%).

Figure 2. Representative images obtained by frequency-domain optical coherence tomography with contrast media and low-molecular-weight dextran L (LMD-L) at the minimum lumen area (MLA) site in (A, B) a patient with a 3.0×13-mm sirolimus-eluting stent (SES) in the left anterior descending artery. Despite guidewire artifact, clear circumferential images could be acquired with both (C) contrast media and (D) LMD-L. MLA was similar between (E) contrast media and (F) LMD-L. *Guidewire artifact.
Statistical Analysis
Statistical analysis was performed using SPSS version 11.0 (SPSS, Chicago, IL, USA). Categorical variables are given as frequencies and were compared using chi-squared test. Continuous variables are presented as mean±SD. Paired Student’s t-test was applied to evaluate differences in serum creatinine and estimated glomerular filtration rate (eGFR) between the 2 groups. The correlation between the 2 methods was analyzed by simple linear regression. The agreement of the FD-OCT image acquisition with contrast and LMD-L was established using Bland-Altman analysis. P<0.05 was considered statistically significant.

Results
Assessment of Image Quality
The total number of segments evaluated was 525 in contrast media and 538 in LMD-L, respectively. The number of CIS was 514 (97.9%) in contrast media and 519 (96.5%) in LMD-L (P=0.90; Table 1). The other parameters for the 25 implanted coronary stents in 22 patients are summarized in Table 2.

Quantitative Assessment
Linear regression analysis and Bland-Altman analysis for minimum LA (MLA), mean LA, and mean SA in 2 pullbacks with contrast media and LMD-L are shown in Figure 3. The correlation coefficients were high for all measurements using the 2 methods (MLA, 6.23±2.26 vs. 6.23±2.25 mm², P=1.00; mean...
LA, 6.81±2.55 vs. 6.75±2.48 mm², P=0.93; mean SA, 7.01±2.58 vs. 6.93±2.50 mm², P=0.91; respectively; Figure 3A). The absolute differences of MLA, mean LA, and mean SA between the 2 pullbacks were 0.09 mm², 0.18 mm², and 0.18 mm², respectively. The lower and upper limits of agreement for MLA, mean LA, and mean SA were –0.21 and 0.22; –0.37 and 0.50; and –0.37 and 0.54, respectively (comparison of contrast media and LMD-L; Figure 3B).

Influence on Renal Function

The total volume of contrast media/LMD-L for image acquisition, and the renal function are summarized in Table 3. The contrast media and LMD-L volume needed to remove the blood for OCT image acquisition was 16.8±1.7 ml and 18.4±4.2 ml, respectively (P=0.10). There were no differences between before and after OCT with respect to renal function (Cr, 0.83±2.24 mg/dl vs. 0.82±0.24 mg/dl, P=0.90; eGFR, 69.9±17.9 ml·min⁻¹·1.73 m⁻² vs. 69.9±16.7 ml·min⁻¹·1.73 m⁻², P=1.00).

No complications related to the OCT procedure (ie, couplet or more, premature ventricular beats, ventricular tachycardia, ST-segment elevation, bradycardia, and chest oppression or pain) occurred.

Physical Property of Each Flushing Medium

The results of viscosity measurement are listed in Table 4. The viscosity of contrast media and LMD-L was 9.40 mm²/s and 3.67 mm²/s, respectively. The viscosity of a mixture of LMD-L and blood (1:1) was similar to that of contrast media and blood (1:1; 4.10 mm²/s and 5.91 mm²/s, respectively).

Discussion

This study was performed to evaluate the quantitative and qualitative differences of FD-OCT image acquisition with LMD-L in comparison to contrast media. We demonstrated that the image quality and lumen measurement of FD-OCT imaging with LMD-L were comparable to those with contrast media. Furthermore, the good correlations between contrast media and LMD-L injections were observed in the measurement of MLA, mean LA, and mean SA. These results suggest that LMD-L has a possibility to be used for FD-OCT image acquisition instead of contrast media in terms of qualitative and quantitative assessment.

FD-OCT may be a useful tool for the guidance of PCI. The FD-OCT system, however, requires injection of contrast media for reliable image acquisition. Although recently developed contrast agents are relatively safer in most patients, contrast-induced acute kidney injury remains 1 of the major causes of in-hospital and long-term morbidity and mortality, particularly in patients with pre-existing renal dysfunction. Therefore, OCT should be indispensable for the assessment of coronary artery disease. The current TD-OCT systems (M2 and M3), however, require vessel occlusion by balloon inflation and vessel flushing to remove blood from the imaging field, because OCT light signals are attenuated by the presence of red blood cells. This can cause myocardial ischemia and/or vessel injury, and the occlusion balloon disturbs assessment of the proximal segments.

The FD-OCT system has recently been found to overcome many of the technical limitations of the conventional TD-OCT system due to the improvement in interrupting blood flow, higher penetration depth, higher frame rate (100 frame/s), and faster imaging acquisition rate (20 mm/s) without loss of image quality, and this technology does not require proximal balloon occlusion, thereby reducing vessel injury. Furthermore, in combination with a short, non-occlusive flush and a faster pullback speed, FD-OCT enables us to acquire images of longer coronary segments without significant ischemia and motion artifacts. FD-OCT may be a useful tool for the guidance of PCI. The FD-OCT system, however, requires injection of contrast media for reliable image acquisition. Although recently developed contrast agents are relatively safe in most patients, contrast-induced acute kidney injury remains 1 of the major causes of in-hospital and long-term morbidity and mortality, particularly in patients with pre-existing renal dysfunction. Hence, it is necessary for us to reduce the total amount of contrast media used as much as possible. Meanwhile, dextran improves OCT penetration of blood and has the potential to reduce the total amount of contrast media when PCI is done under OCT guidance. FD-OCT may be helpful for patients with renal dysfunction, if we can assess the culprit lesion characteristics and the post-stent abnormalities using LMD-L in place of contrast media. Consequently, we might be able to use FD-OCT with LMD-L repeatedly, for PCI guidance, even when patients have renal insufficiency.

LMD-L has been used as the flushing medium for coronary angioplasty and we successfully observed culprit lesion with TD-OCT using LMD-L without any serious complications. A previous experimental study reported that dextran is the best OCT flushing medium compared with X-ray contrast or saline. The viscosity of LMD-L is 3.67 mm²/s, which is high enough to remove blood cells, and the osmolality ratio to saline of LMD-L is 1.0. In addition to the clinical use experience and physical properties of LMD, LMD-L includes potassium (4 mmol/L), which could prevent fatal arrhythmia during coronary injection. Although a previous study demonstrated that LMD itself had no nephrotoxic potential and was not filtered by the kidney, LMD might influence the reabsorption of fluid at renal tubules in hypovolemia. Therefore, it would be necessary to monitor hypovolemic status when LMD-L is used for OCT.

<table>
<thead>
<tr>
<th>Table 4. Physical Properties of Flushing Media</th>
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<tbody>
<tr>
<td>Solution</td>
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<tr>
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<tr>
<td>Contrast media (Omnipaque® 350)</td>
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<tr>
<td>LMD-L</td>
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<tr>
<td>Contrast media and blood (1:1)</td>
</tr>
<tr>
<td>LMD-L and blood (1:1)</td>
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</table>

*Manufacturer’s specification. For comparison, the viscosity of human whole blood at hematocrit 0.51 is 4.51 mm²/s. LMD-L, low-molecular-weight dextran L.
Study Limitations
In addition to the type of flushing solution, the infusion rate of each solution may affect image quality. LightLab Imaging recommends a contrast injection rate of 4 ml/s for left coronary artery (LCA) and 3–3.5 ml/s for right coronary artery (RCA), while the optimal infusion rate of LMD-L for OCT image acquisition has not been established. Regarding the infusion rate of both LMD-L and contrast, we used the same rate to obtain FD-OCT images in both LCA and RCA in the present study. The rate of 4 ml/s, however, may be inadequate for LMD-L, which has a lower viscosity, especially in the LCA, which has more side branches and greater perfusion territory than the RCA. Therefore, in the near future, further investigations are required to clarify the appropriate amount of LMD-L in each vessel.

Conclusions
FD-OCT with LMD-L produced the same image quality and provided excellent quantitative assessment compared to that with contrast media. FD-OCT with LMD-L may have the potential to reduce the total amount of contrast media without loss of image quality. In the near future, it is expected that FD-OCT image acquisition with LMD-L will be more widely adopted in clinical practice, especially in patients with renal insufficiency.

Acknowledgment
There are no conflicts of interest in this study.

References