Quantitative Ex Vivo and In Vivo Comparison of Lumen Dimensions Measured by Optical Coherence Tomography and Intravascular Ultrasound in Human Coronary Arteries

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Introduction and objectives. The relationship between the lumen dimensions obtained in human coronary arteries using intravascular ultrasound (IVUS) and those obtained using optical coherence tomography (OCT) is not well understood. The objectives were to compare the lumen measurement obtained ex vivo in human coronary arteries using IVUS, OCT, and histomorphometry, and in vivo in patients using IVUS and OCT with and without balloon occlusion.

Methods. Ex vivo study: the lumen areas of matched anatomical sections of human coronary arteries were measured using IVUS, OCT, and histology. In vivo study: the lumen areas in matched sections were measured using IVUS and OCT with and without occlusion.

Results. Ex vivo: in the 8 specimens studied, the lumen area obtained using OCT and IVUS was larger than that obtained using histomorphometry: mean difference 0.8 (1) mm² (28%) for OCT and 1.3 (1.1) mm² (40%) for IVUS. In vivo: in the 5 vessels analyzed, the lumen area obtained using IVUS was larger than that obtained using OCT: mean difference 1.67 (0.54) mm² (33.7%) for IVUS relative to OCT with occlusion and 1.11 (0.53) mm² (21.5%) relative to OCT without occlusion. The lumen area obtained using OCT without occlusion was larger than that obtained using OCT with occlusion: mean difference 0.61 (0.23) mm² (13%).

Conclusions. In fixed human coronary arteries, both IVUS and OCT overestimated the lumen area compared with histomorphometry. In vivo the lumen dimensions obtained using IVUS were larger than those obtained using OCT, with or without occlusion. Moreover, the OCT image acquisition technique (ie, with or without occlusion) also had an impact on lumen measurement.

Key words: Optical coherence tomography. Intravascular ultrasound. Lumen dimensions. Ex vivo. In vivo. Intracoronary imaging.

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ABBRÉVIATIONS
IVUS: intravascular ultrasound
LAD: left anterior descending coronary artery
LCX: left circumflex artery
MLA: minimum lumen area
OCT: optical coherence tomography

INTRODUCTION
Optical coherence tomography (OCT) is a new intracoronary imaging modality that provides in vivo high-resolution images of the coronary artery. The OCT imaging technique is, in general, similar to that of intravascular ultrasound (IVUS), but whereas IVUS works by applying radiofrequency radiation, OCT uses light radiation. In both techniques the imaging probe is automatically pulled back through the coronary segment of interest. In contrast to IVUS, in OCT acquisition the coronary vessel needs to be cleared of blood. This is necessary since red blood cells are non-transparent causing multiple light scattering and substantial signal attenuation. This was achieved in the first commercially available OCT system by proximal occlusion of the vessel with a dedicated low-pressure balloon and simultaneous distal flush delivery (occlusive technique) during OCT probe pullback. However, the recent increase in pullback speed (from 1 mm/s to 3 mm/s) enabled OCT pullback while displacing blood by continuous flush (x-ray contrast medium) delivery through the guide catheter without the need for vessel occlusion (non-occlusive technique). The impact of these 2 different acquisition techniques on lumen dimension when measured by OCT has not yet been reported.

The present study had 2 aims: to compare lumen size when measured by IVUS, OCT and histology in human coronary arteries ex vivo; to compare, in vivo, intracoronary lumen size when measured in patients by OCT with balloon occlusion, OCT without balloon occlusion, and IVUS.

METHODS
Ex Vivo Human Coronary Arteries

Specimens
Ten left anterior descending coronary artery (LAD) segments were excised within 24 h post-mortem, 1 cm proximal to the bifurcation with the left circumflex artery (LCX) and fixed in 4% formaldehyde. Standard 6 F coronary sheaths (Arrow, Reading, PA, USA) were introduced and fixed at the distal and proximal ends of the arteries.

Intracoronary Imaging
For intracoronary imaging, the specimens were immersed in a saline bath at room temperature and perfused with saline at physiologic pressure. IVUS data were acquired using the Atlantis™ 40 MHz catheter with an automated motorized pullback device at a constant speed of 0.5 mm/s. OCT data were acquired using a commercially available system for intracoronary imaging and a 0.019” ImageWire™ (LightLab Imaging, Westford, MA, USA) with automated pullback at 1 mm/s. Lumen measurements in both IVUS and OCT were performed with the same dedicated coronary vessel analysis software (CURAD, Wijk bij Duurstede, Netherlands).

Histology Preparation and Analysis
Following the intracoronary imaging procedures, the specimens were sectioned for histological analysis. The distal side of the bifurcation of the LAD to the LCX was used as the starting point for the first histology section. From this point to the distal and proximal side, histology sections were taken at 5-mm intervals to the end of the specimen.

Matching Procedure
The OCT and IVUS pullbacks were matched by vessel analysis software (CURAD), which can synchronize image data acquired with different modalities onto a single computer screen. The proximal and distal sheaths were used as longitudinal landmarks. After histology tissue processing, the sections (e.g., microscopic images) were used to identify the corresponding location in the OCT image data set based on the similar visual appearance of the lumen morphology. Following this identification process, the visualization software synchronized the OCT and the IVUS image data sets and identified the corresponding IVUS image (Figure 1). To avoid the Dotter effect, only cross-sections where the IVUS catheter was moving freely in the lumen were selected.

In Vivo Human Coronary Arteries

Study Population
Patients who were undergoing OCT examination of 1 coronary artery were included in the study. The medical ethics committee of the Erasmus MC
Non-occlusive technique: the ImageWire was placed in the artery using a double lumen catheter (Twin Pass catheter, Vascular Solutions). Pullback was performed during continuous injection of contrast medium (3 mL/s, Iodixanol 370, Visipaque, GE Health Care, Cork, Ireland) through the guide catheter with an injection pump. In this case, the automated pullback rate was 3 mm/s.

The lumen measurements were performed with proprietary software for offline analysis (LightLab Imaging, Westford, MA, USA). For all OCT studies, the settings for the refraction index were adjusted to the flush solution used (saline, Ringer's lactate, and x-ray contrast, respectively).

Matching of OCT and IVUS Pullbacks

The region of interest was matched in the 3 pullbacks (occlusive OCT, non-occlusive OCT, and IVUS) using landmarks such as side branches (Figure 2). Differences in pullback speed were adjusted to appropriately compare the 2 OCT pullbacks per frame.

Statistical Analysis

Statistical analysis was performed using SPSS 12.0.1 for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean (standard deviation) and categorical variables are expressed as percentages. The absolute and relative differences between measurements obtained with the different techniques were calculated. The relative difference was defined as the absolute difference divided by the average. Data are also expressed in

Figure 1. Matching of IVUS, OCT, and histology ex vivo. The distal side of the bifurcation of the LAD to the LCX (*) was used as the starting point for the first histology section. From this point to the distal and proximal side, histology sections were taken at 5-mm intervals to the end of the specimen (A). The histology sections (B) were used to identify the corresponding location in the OCT image data set (C) based on the similar visual appearance of the lumen morphology. Following this identification, the visualization software synchronized the OCT and IVUS image data sets and identified the corresponding IVUS image (D).
was obtained in 35 frames. Overall, the mean lumen, plaque and vessel area when measured by histomorphometry were 2.5 (1.7) mm$^2$, 3.7 (1.9) mm$^2$, and 7.6 (3.2) mm$^2$, respectively. The mean percentage of stenosis was 59% (18%).

Bland-Altman and regression analyses were performed on the lumen area measurements between the 3 imaging modalities (Figure 3). The average relative differences of the lumen measurements were 28% between OCT and histology, 40% between IVUS and histology, and 11% between IVUS and OCT.

In Vivo Human Coronary Arteries

Clinical and Procedural Characteristics

Five patients (5 vessels) were included in the study. The average age was 61.2 (8.9) years and 4/5 were male. Three out of 5 had hypertension, 1 of 5 had diabetes, 4 of 5 had hyperlipidemia, and none were smokers. The imaged vessel was the LAD in 1 case and the LCX in the other 4 cases. Only 1 patient presented chest pain and ST depression during acquisition with balloon occlusion, which disappeared immediately after balloon deflation.

Comparison Lumen Measurements With OCT and IVUS

Overall, the mean lumen, plaque, and vessel area measured by IVUS were 6.3 (1.0) mm$^2$, 6.9 (1.4) mm$^2$, and 13.3 (1.7) mm$^2$, and mean cross-sectional area stenosis was 52% (6%).

Comparison IVUS and OCT With Occlusion

The mean relative difference for the mean lumen area was 33.7%, and the mean absolute difference for the mean lumen area was 1.67 (0.54) mm$^2$, with limits of agreement of 0.62-2.73 mm$^2$ (Table 1). The mean relative difference for the minimum lumen area (MLA) between IVUS and OCT with occlusion was 55.5%, and the mean absolute difference was 1.90 (0.37) mm$^2$, with limits of agreement 0.37-2.63 mm$^2$.

Comparison IVUS and OCT Without Occlusion

The average relative difference for the mean lumen area was 21.5%, and the absolute difference was 1.11 (0.53) mm$^2$, with limits of agreement of 0.05-2.14 mm$^2$ (Table 2). The average relative difference for MLA was 29%, and the average absolute difference was 1.10 (0.37) mm$^2$, with limits of agreement 0.37-1.83 mm$^2$.

RESULTS

Ex Vivo Human Coronary Arteries

Intravascular ultrasound and OCT were successfully performed in 8 out of 10 specimens. Intracoronary imaging was not possible in 2 cases due to the lumen being totally occluded. A good match between OCT, IVUS, and histology images

Bland-Altman plots showing the absolute difference between corresponding lumen measurements for both techniques (y-axis) versus the average of both techniques (x-axis). The limits of agreement were calculated as the mean difference (+2SD).
Figure 3. Lumen measurements in ex vivo coronary arteries. Bland-Altman plots showing the differences in lumen measurements between OCT and histology (A), IVUS and histology (B), and OCT and IVUS (C). Correlation for lumen measurements between OCT and histology (A’), IVUS and histology (B’), and OCT and IVUS (C’).

### TABLE 1. Differences in the Mean and Minimum Lumen Area (MLA) Between IVUS and OCT Pullbacks Acquired With the Occlusive technique

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mean Lumen Area IVUS, mm²</th>
<th>Mean Lumen Area OCT Occlusion, mm²</th>
<th>Absolute Difference, mm²</th>
<th>Difference %</th>
<th>MLA IVUS, mm²</th>
<th>MLA OCT Occlusion, mm²</th>
<th>Absolute Difference, mm²</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.57 (0.93)</td>
<td>3.40 (0.89)</td>
<td>2.17</td>
<td>48.50</td>
<td>4.04</td>
<td>1.89</td>
<td>2.15</td>
<td>72.51</td>
</tr>
<tr>
<td>2</td>
<td>6.76 (0.73)</td>
<td>5.53 (0.75)</td>
<td>1.23</td>
<td>20.02</td>
<td>5.33</td>
<td>3.74</td>
<td>1.59</td>
<td>35.06</td>
</tr>
<tr>
<td>3</td>
<td>7.81 (0.74)</td>
<td>6.58 (0.95)</td>
<td>1.23</td>
<td>17.09</td>
<td>6.35</td>
<td>4.91</td>
<td>1.44</td>
<td>25.58</td>
</tr>
<tr>
<td>4</td>
<td>5.21 (0.53)</td>
<td>2.87 (0.55)</td>
<td>2.34</td>
<td>57.77</td>
<td>4.10</td>
<td>1.78</td>
<td>2.32</td>
<td>78.91</td>
</tr>
<tr>
<td>5</td>
<td>6.19 (2.32)</td>
<td>4.81 (2.29)</td>
<td>1.38</td>
<td>25.06</td>
<td>4.06</td>
<td>2.05</td>
<td>2.01</td>
<td>65.79</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).
TABLE 2. Differences in the Mean and Minimum Lumen Area (MLA) Between IVUS and OCT Pullbacks Acquired With the Non-occlusive Technique

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mean Lumen Area IVUS, mm²</th>
<th>Mean Lumen Area OCT Non-occlusion, mm²</th>
<th>Absolute Difference, mm²</th>
<th>% Difference</th>
<th>MLA IVUS, mm²</th>
<th>MLA OCT Non-occlusion, mm²</th>
<th>Absolute Difference, mm²</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.57 (0.93)</td>
<td>3.83 (0.72)</td>
<td>1.74</td>
<td>37.04</td>
<td>4.04</td>
<td>2.76</td>
<td>1.28</td>
<td>37.65</td>
</tr>
<tr>
<td>2</td>
<td>6.76 (0.73)</td>
<td>5.90 (0.63)</td>
<td>0.86</td>
<td>13.59</td>
<td>5.33</td>
<td>4.16</td>
<td>1.17</td>
<td>24.66</td>
</tr>
<tr>
<td>3</td>
<td>7.81 (0.74)</td>
<td>7.39 (1.01)</td>
<td>0.42</td>
<td>5.52</td>
<td>6.35</td>
<td>5.86</td>
<td>0.49</td>
<td>8.02</td>
</tr>
<tr>
<td>4</td>
<td>5.21 (0.53)</td>
<td>3.68 (0.55)</td>
<td>1.53</td>
<td>34.47</td>
<td>4.10</td>
<td>2.81</td>
<td>1.49</td>
<td>44.41</td>
</tr>
<tr>
<td>5</td>
<td>6.19 (2.32)</td>
<td>5.24 (2.08)</td>
<td>0.95</td>
<td>16.70</td>
<td>4.06</td>
<td>2.99</td>
<td>1.07</td>
<td>30.35</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).

**Comparison of the Lumen Measurements by OCT With and Without Occlusion**

For the comparison of lumen dimensions when measured by OCT, 373 matched frames obtained with and without occlusion were analyzed (Figure 4). The mean length of the region analyzed was 11.34 (3.87) mm with occlusion and 11.23 (3.86) mm without occlusion \((P=.96)\). Bland-Altman and regression analyses were also performed for these measurements (Figure 5).

The mean absolute and relative differences for mean lumen area were 0.61 (0.23) mm² (13%) (limits of agreement, 0.15-1.07 mm²). The mean absolute and relative differences for MLA were 0.80 (0.21) mm² (28%) (limits of agreement, 0.37-1.23 mm²) (Tables 3 and 4).
Figure 5. Comparison of lumen measurements with optical coherence tomography (OCT) with and without occlusion. Bland-Altman plot showing the differences between lumen measurements in OCT pullbacks acquired with the occlusive and non-occlusive technique (A). Correlation between the lumen measurements in the OCT pullbacks acquired with and without occlusion (B).

### TABLE 3. Differences in the Mean Lumen Area Between OCT Pullbacks Acquired With the Occlusive and Non-Occlusive Technique

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mean Lumen Area Occlusive, mm²</th>
<th>Mean Lumen Area Non-occlusive, mm²</th>
<th>Absolute Difference, mm²</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.40 (0.89)</td>
<td>3.83 (0.72)</td>
<td>0.43</td>
<td>12.00</td>
</tr>
<tr>
<td>2</td>
<td>5.73 (0.89)</td>
<td>6.20 (0.95)</td>
<td>0.47</td>
<td>7.87</td>
</tr>
<tr>
<td>3</td>
<td>6.58 (0.95)</td>
<td>7.39 (1.01)</td>
<td>0.81</td>
<td>11.58</td>
</tr>
<tr>
<td>4</td>
<td>3.10 (0.78)</td>
<td>4.02 (0.91)</td>
<td>0.92</td>
<td>25.90</td>
</tr>
<tr>
<td>5</td>
<td>4.81 (2.29)</td>
<td>5.24 (2.08)</td>
<td>0.42</td>
<td>8.45</td>
</tr>
<tr>
<td>Average</td>
<td>4.72 (1.49)</td>
<td>5.34 (1.49)</td>
<td>0.61 (0.23)</td>
<td>13.16</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).

### TABLE 4. Differences in the Minimum Lumen Area (MLA) Between OCT Pullbacks Acquired With the Occlusive Non-occlusive Technique

<table>
<thead>
<tr>
<th>Vessel</th>
<th>MLA occlusive, mm²</th>
<th>MLA Non-occlusive, mm²</th>
<th>Absolute Difference, mm²</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.89</td>
<td>2.76</td>
<td>0.87</td>
<td>37.42</td>
</tr>
<tr>
<td>2</td>
<td>3.74</td>
<td>4.16</td>
<td>0.42</td>
<td>10.63</td>
</tr>
<tr>
<td>3</td>
<td>4.91</td>
<td>5.86</td>
<td>0.95</td>
<td>17.64</td>
</tr>
<tr>
<td>4</td>
<td>1.78</td>
<td>2.61</td>
<td>0.83</td>
<td>37.81</td>
</tr>
<tr>
<td>5</td>
<td>2.05</td>
<td>2.99</td>
<td>0.94</td>
<td>37.30</td>
</tr>
<tr>
<td>Average</td>
<td>2.87 (1.39)</td>
<td>3.67 (1.36)</td>
<td>0.80 (0.21)</td>
<td>28.16</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD).
The mean lumen volumes were 55 (29.5) and 60.4 (30.4) mL³ with and without occlusion, respectively, with a relative difference of 11.7%. The mean absolute difference was 5.4 (2.7) mL³ and the limits of agreement were 0.0-10.7 mm³.

DISCUSSION

Optical coherence tomography is emerging as one of the most promising intracoronary imaging modalities due to its capacity to provide very high-resolution images of the coronary vessel wall. It enables the very detailed assessment of atherosclerotic plaque and the interaction between implanted coronary stents and the vessel wall.¹⁰,¹¹ In recent years, there has been continuous technical development that has led to changes in the OCT acquisition technique (changing from the need to occlude the vessel to a non-occlusive procedure) which have simplified the use of the technology and reduced patient discomfort.¹²,¹³ However, even though the non-occlusive technique is currently gradually replacing the occlusive technique in many centers, it remains “off-label.” Furthermore, many of the recently published OCT data were obtained by using the occlusive technique.¹⁴,²⁰ The impact of the acquisition technique in relation to quantitative lumen measurements obtained by OCT and compared to quantitative IVUS has not yet been reported. The present study showed the following: a) in fixed human coronary arteries, both OCT and IVUS overestimated the lumen area compared to histology; b) lumen dimensions when measured by IVUS are larger than those when measured by OCT with or without occlusion in vivo; and c) the OCT acquisition technique (occlusive or non-occlusive) has an impact on lumen dimension measurements.

Differences in Lumen Measurements Between IVUS, OCT, and Histology

In the present study, the lumen areas when measured by IVUS and OCT were larger than those measured by histology in fixed human coronary arteries. The mean differences with histomorphometry were 0.8 mm² (28%) for OCT and 1.3 mm² (40%) for IVUS. These results are in line with a previous study in stented porcine coronary arteries that showed that lumen area was largest when measured by IVUS, followed by OCT, and was smallest when measured by histology.²¹ However, it should be borne in mind that the ex vivo processing of the specimen for histology analysis may have had an influence on lumen size. It is well established that
tissue shrinkage occurs in different phases when preparing specimens for histology.22 Regarding the comparison of IVUS and OCT, our in vivo data are in agreement with the ex vivo findings. In our study, the lumen dimensions measured by IVUS in living patients were always higher than those measured by OCT with or without balloon occlusion. There are several studies in the literature comparing lumen dimensions measured by IVUS and OCT with occlusion that show contrasting results. Kawase et al. performed IVUS and OCT with occlusion in vivo in 6 coronary arteries in pigs and reported no differences in lumen areas and volumes between IVUS and OCT with occlusion.23 However, another study in pigs with a larger sample size reported an absolute difference of 0.49 mm² between mean lumen area by IVUS and OCT acquired with the occlusive technique in stented segments.21 Yamaguchi et al. evaluated in vivo differences in humans and found that the MLA was significantly smaller when measured by OCT with occlusion than when measured with IVUS (mean difference, 0.4 mm²). The greater differences found in our data could be explained by the fact that we did not include coronary segments treated with bare-metal stents. Bare-metal stents are probably less affected by variations in intracoronary pressure caused by proximal vessel occlusion as they have considerable radial strength.

To our knowledge, no published studies have reported differences in measurements between IVUS and OCT acquired with the non-occlusive technique. In the present study, the lumen dimensions were even larger by IVUS, but the differences, as expected, were smaller than with occlusion.

The greater overestimation of lumen dimensions when measured by IVUS compared to OCT could be related to the difficulty in differentiating the lumen border by IVUS due to blood speckle or presence of artefacts.24 OCT shows the lumen-intima interface as a sharply defined border, clearly visible in most cases.25 IVUS also overestimates the lumen area compared to quantitative angiography measurements (both by videodensitometry and edge detection).26-28 In our study, the differences between lumen measurements by IVUS and OCT were higher in vivo than ex vivo. This could be related to the frame selection for in vivo analysis. The IVUS pullback obtained in vivo was processed with a gating system that selects end-diastolic frames (the moment in the cardiac cycle when the vessel is biggest), whereas OCT pullback is not gated and therefore the frames could correspond to any moment in the cardiac cycle. Previous IVUS studies have suggested a variation in lumen area during the cardiac cycle in the range of 8%.29

The differences found between lumen size when measured by IVUS and OCT may have clinical implications if OCT is going to be used to define lesion severity. An MLA <4 mm² has been associated with myocardial ischemia and has been considered a criterion for coronary lesion revascularization. In the present study, whereas all the patients had an MLA >4 mm² when measured by IVUS, 4 out of 5 patients had an MLA <4 mm² when measured by OCT with occlusion. All the patients were asymptomatic and were not treated. This reinforces the idea that IVUS criteria cannot be directly translated to OCT and emphasizes the need for new specific cut-off points to define lesion severity by OCT.

Impact of OCT Acquisition Technique on Lumen Measurements

The present report consistently shows that the mean and minimum lumen areas were smaller when OCT was performed with balloon occlusion than acquisitions without occlusion. These differences could be related to the decrease of intracoronary pressure due to the vessel occlusion that is not completely compensated by continuous flush injection. Furthermore, the injection of contrast medium during the non-occlusive procedure increases intracoronary pressure (Figure 6). These phenomena are likely to be more accentuated in healthy arteries and in coronary segments not treated with bare-metal stents (as in this study). The relative differences were higher in smaller vessels, suggesting that they may have a greater tendency to collapse after occlusion.

Limitations

Even though a complex matching process was used, the difference in slice thickness between IVUS, OCT, and histology cross-sections may have influenced the results of the ex vivo study. The main limitations of the in vivo study are the small sample size and the limited type of coronary segments that could be analyzed. More data are needed to evaluate the quantitative differences between OCT pullbacks acquired with different techniques and IVUS in human coronary arteries treated with bare-metal stents. Further studies with a larger sample size and using different types of coronary segments are warranted before definite conclusions can be drawn.

CONCLUSION

In fixed human coronary arteries, both OCT and IVUS overestimated lumen areas compared to histomorphometry. Lumen dimensions measured by IVUS are larger than those measured by OCT with or without occlusion in vivo. The OCT acquisition
technique (occlusive or non-occlusive) has an impact on quantitative lumen dimension measurements.

REFERENCES


