Prediction of Chronic Vessel Enlargement by a Novel Intravascular Ultrasound Finding – Peri-Medial High-Echoic Band –

Yoji Neishi, MD; Hiroyuki Okura, MD; Teruyoshi Kume, MD; Kenzo Fukuhara, MD; Ryotaro Yamada, MD; Kiyoshi Yoshida, MD

Background: Coronary arterial segments distal to the severely stenotic lesion sometimes shrink as a result of decreased coronary flow. Pathological studies have shown that vessel shrinkage is accompanied by folding of the internal elastic membrane (IEM). A peri-medial high-echoic band (PHB) by intravascular ultrasound (IVUS) may represent folding of the IEM and therefore detect chronically shrunk coronary segments that have potential to enlarge subsequently.

Methods and Results: IVUS imaging of the distal reference segments was performed in 27 patients after stenting. PHB was defined as a high-echoic band observed at the luminal side of the media. Serial (baseline and 9 months) changes in minimal lumen diameter (LD) were compared between those with (PHB group) and without PHB (non-PHB group). During follow-up, LD increased significantly in PHB group (1.2±0.3 vs. 1.7±0.5 mm, P=0.001) but not in the non-PHB group (2.0±0.7 vs. 2.1±0.7 mm, P=NS). Late lumen gain (LLG) was observed in 16 of the 27 (59%) lesions. Lesions with LLG showed a trend toward smaller baseline lumen cross-sectional area and significantly higher prevalence of PHB (88% vs. 18%, P=0.007). By multivariable logistic regression analysis, PHB was the only IVUS predictor of LLG.

Conclusions: Presence of PHB on IVUS predicts chronic enlargement of the coronary segments distal to the stented lesion. (Circ J 2015; 79: 607–612)

Key Words: Intravascular ultrasound; Percutaneous coronary intervention; Stents

Coronary arterial segments distal to the severely stenotic or occluded lesion usually shrink as a result of chronically decreased coronary flow. Although differentiation of residual organic stenosis and vessel shrinkage that has the potential to reverse without additional intervention is clinically important in the catheterization laboratory, no specific angiographic, intravascular ultrasonographic or optical coherence tomographic findings have been shown.

Recent pathological studies have suggested that vessel spasm or shrinkage is accompanied by folding of the internal elastic membrane (IEM). Intravascular ultrasound (IVUS) may visualize the folding of the IEM as a high-echoic band and thus detect chronically shrunk vessels that have potential to enlarge late after revascularization.

We hypothesized that a novel IVUS finding, a peri-medial high-echoic band (PHB), would predict chronic vessel enlargement of the distal coronary segments after intervention of the severely stenotic proximal target lesion.

Methods

A total of 27 patients who underwent successful IVUS-guided percutaneous coronary intervention (PCI) for severe coronary stenosis were retrospectively selected and enrolled from our IVUS database. Inclusion criteria were lesions with chronic total occlusion (CTO) or severely stenotic lesions (%diameter stenosis >90% and delayed distal flow) with angiographic follow-up at 9 months. Exclusion criteria were culprit lesions for acute myocardial infarction, lesions without final IVUS imaging of the distal reference segments and presence of target lesion restenosis or re-occlusion at follow-up. All patients gave written informed consent.

Angiography and Interventional Procedures

After intravenous or intraarterial bolus injection of heparin (5,000–10,000 units), coronary angiography (CAG) and the PCI were performed by standard femoral or radial approach.
IVUS Procedure and Measurements

After intracoronary nitroglycerin (200 μg) or isosorbide dinitrate (2 mg) injection, IVUS imaging was performed before and/or after PCI in all patients, because IVUS was routinely used for guidance of the PCI procedure in this hospital. A commercially available mechanical rotating 40-MHz IVUS catheter (ViewIT™, Terumo Corp, Tokyo, Japan) and a digital processing IVUS console (VISIWAVE™, Terumo) were used in this study. IVUS imaging of the distal reference was performed in 27 target vessels after successful PCI. IVUS pullback imaging was performed using an automated pullback device at a speed of 0.5 mm/s. IVUS images were digitally recorded for later off-line analysis. On CAG, segments with luminal narrowing of at least 5 mm distal to the stent edge were selected for IVUS analysis. If focal luminal narrowing was not present, the cross-section with the largest external elastic membrane cross-sectional area (EEM CSA) was selected for IVUS analysis. Using commercially available planimetry software (VISIATLAS™, Terumo), the EEM CSA and lumen CSA were measured. Plaque plus media (P+M) CSA was calculated as the difference between EEM CSA and lumen CSA.

Plaque burden was calculated as P+M CSA/EEM CSA × 100 (%).

PHB was defined as a high-echoic band observed at the luminal side of the media (Figure 1). Lesions with PHB on IVUS in at least 3 consecutive frames were classified as the PHB group.

Quantitative CAG (QCA)

Off-line quantitative analysis of CAG was performed with the CAAS II system (Pie Medical Imaging, Maastricht, The Netherlands), blinded to clinical as well as IVUS findings. Minimal lumen diameter (LD) of the distal reference segment was measured. Both QCA and IVUS measurements were done for the same segments. IVUS and angiographic images were co-registered using side branch and stent edge as landmarks. Serial (baseline and 9 months) changes in LD were compared between those with (PHB group) and without PHB (non-PHB group).
Quantitative IVUS, lesions with LLG showed a trend toward smaller baseline lumen CSA (P=0.07) and larger plaque burden (P=0.08) compared with lesions without LLG. PHB was more frequently detected in lesions with LLG than in lesions without LLG.

**Table 2. Lesion and Procedural Characteristics of Patients Who Underwent Successful IVUS-Guided PCI for Severe Coronary Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>PHB (n=16)</th>
<th>Non-PHB (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA</td>
<td>8/5/3</td>
<td>6/0/5</td>
<td>0.257</td>
</tr>
<tr>
<td>CTO lesion, n (%)</td>
<td>16 (100)</td>
<td>6 (55)</td>
<td>0.017</td>
</tr>
<tr>
<td>Stent type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS/DES</td>
<td>2/12</td>
<td>2/9</td>
<td>0.523</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>2.7±0.4</td>
<td>2.8±0.5</td>
<td>0.474</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>34±19</td>
<td>39±23</td>
<td>0.646</td>
</tr>
<tr>
<td>Stent number, n</td>
<td>1.5±1.0</td>
<td>1.5±0.8</td>
<td>0.865</td>
</tr>
</tbody>
</table>

BMS, bare-metal stent; CTO, chronic total occlusion; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. Other abbreviations as in Table 1.

**Table 3. IVUS Results of Patients Who Underwent Successful IVUS-Guided PCI for Severe Coronary Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>PHB (n=16)</th>
<th>Non-PHB (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEM CSA, mm²</td>
<td>8.3±4.9</td>
<td>9.3±4.5</td>
<td>0.512</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>4.4±2.1</td>
<td>6.1±3.5</td>
<td>0.357</td>
</tr>
<tr>
<td>P+M CSA, mm²</td>
<td>3.8±3.2</td>
<td>3.1±1.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>42±11</td>
<td>35±16</td>
<td>0.060</td>
</tr>
</tbody>
</table>

CSA, cross-sectional area; EEM, external elastic membrane; P+M, plaque plus media. Other abbreviations as in Table 1.

**Results**

PHB was detected in 16 lesions (59%). In the PHB group, PHB was also detected in other vessel segments, but in the non-PHB group, PHB was not detected at all. The clinical characteristics of the patients in both groups are summarized in Table 1, but there were no significant differences between them for these and for lesion and procedural characteristics (Table 2), except for a higher prevalence of CTO lesions in the PHB group. Baseline IVUS results are shown in Table 3. EEM, lumen and P+M CSA were similar between the 2 groups, but plaque showed a trend toward greater burden in the PHB group than in the non-PHB group, although the difference did not reach statistical significance (P=0.06).

During follow-up (median 252 days), LD increased significantly in the PHB group (1.2±0.3 to 1.7±0.5 mm, P=0.001), but did not change over time in the non-PHB group (2.0±0.7 to 2.1±0.7 mm, P=NS) (Figure 2). The percent change in LD was significantly greater in the PHB group than in the non-PHB group (+50% vs. +7%, P=0.001).

IVUS indices were also compared between lesions with and without Late lumen gain (LLG) (Table 4), which was defined as ([LD at follow-up]–[LD at baseline])/[LD at baseline] ×100 ≥0.1. LLG was documented in 16 of 27 (59%) lesions. By quantitative IVUS, lesions with LLG showed a trend toward smaller baseline lumen CSA (P=0.07) and larger plaque burden (P=0.08) compared with lesions without LLG. PHB was more frequently detected in lesions with LLG than in lesions without LLG.

Statistical Analysis

Data are expressed as the mean±SD for continuous variables and as frequency (%) for categorical variables. Unpaired t-test was performed to compare continuous variables, and the chi-square test or Fisher’s exact test was used to compare categorical variables. Paired t tests were performed to compare the data at baseline and after stent implantation of both groups. A P-value <0.05 was considered to be statistically significant. Analyses were performed in part with StatView 5.0 (SAS Institute, Cary, NC, USA).
Discussion

Principal findings of this study were that IVUS detected PHB in 59% of the distal, unstented segments after successful coronary revascularization. Lumen diameter of the lesions with PHB significantly increased at 9-month follow-up. Presence of PHB was a single IVUS predictor of LLG.

It is well known that the lumen size of the reference segments distal to the chronically occluded or severely stenotic lesion may increase late after successful PCI of the culprit lesion. A recent serial IVUS observational study, as well as an angiographic follow-up study, demonstrated that the lumen area of the distal reference segments increases in 69% of the patients with successful recanalization of CTO at 6-month follow-up. Our results showing that LLG was detected in 59% of lesions are concordant with that. Although others did not find an IVUS predictor of LLG, we identify a novel IVUS finding, PHB, as the single best predictor of LLG.

Table 4. IVUS Comparison of Lesions With and Without LLG in Patients Who Underwent Successful IVUS-Guided PCI for Severe Coronary Stenosis

<table>
<thead>
<tr>
<th></th>
<th>LLG (+) (n=16)</th>
<th>LLG (-) (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEM CSA, mm²</td>
<td>7.8±4.6</td>
<td>9.9±4.7</td>
<td>0.292</td>
</tr>
<tr>
<td>Lumen CSA, mm²</td>
<td>4.1±1.8</td>
<td>6.7±3.4</td>
<td>0.071</td>
</tr>
<tr>
<td>P+M CSA, mm²</td>
<td>3.8±3.2</td>
<td>3.2±1.5</td>
<td>0.845</td>
</tr>
<tr>
<td>Plaque burden, %</td>
<td>43±15</td>
<td>33±10</td>
<td>0.082</td>
</tr>
<tr>
<td>PHB, n (%)</td>
<td>14 (88)</td>
<td>2 (18)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

LLG, late lumen gain. Other abbreviations as in Tables 1,3.
Park et al and Ogita et al reported clinical or angiographic predictors of LLG, but we did not find similar findings. Recent pathological studies have suggested a possible role of the IEM and media in coronary arterial lesions with spasm or vessel shrinkage. Mortensen et al reported folding of the IEM during coronary spasm. Furthermore, Uchida et al demonstrated both folding of the IEM and thickening of the media during coronary spasm. Folding of the IEM may enhance ultrasonic backscatter signal from the luminal border of the media, which is characterized as a low-echoic or sonolucent circular band. Coronary segments distal to the CTO lesion or severe stenosis with delayed distal flow typically show vessel shrinkage because of decreased perfusion pressure and impaired flow-mediated vasodilatation. Even after successful revascularization of the target lesion, the vessel may not dilate immediately because of impaired endothelial function. In our study, intracoronary nitrates were administered before CAG or IVUS imaging. Therefore, not only endothelium-dependent but also endothelium-independent vessel dilatation of the distal segments may be impaired.

Vessel shrinkage may occur during coronary spasm or compression of the coronary artery by a myocardial bridge. Coronary spasm can be excluded by the administration of nitrates. However, it may be difficult to differentiate between intractable vasospasm and chronic vessel shrinkage. On the other hand, myocardial bridge may be excluded based on the presence of an ultrasonic echolucent band surrounding the coronary artery and the cyclic compression of the coronary artery during systole.

Clinically, it is necessary to decide whether or not to treat residual stenosis of the distal reference segments after revascularization of the target lesion. Because 60–70% of the distal segments enlarge subsequently without additional intervention, it is important to detect and predict the natural course of the distal segments to avoid unnecessary intervention. Additional stenting of the distal segments has several problems. First, it is costly. Second, it may cause dissection of the very distal edge of the additional stent. Third, additional deployment of a small and long stent may have higher risk for subsequent stent thrombosis as well as stent restenosis. Fourth, late incomplete stent apposition may occur as a result of late vessel enlargement. Finally, it may abolish the chance of future bypass grafting. Our present results therefore have the strong clinical implication that based on the presence or absence of PHB, we can safely defer additional and probably unnecessary intervention. Vice versa, additional stenting may be indicated for residual stenosis if PHB is not detected by IVUS. In our study, although the baseline LD was different between lesions with and without PHB, difference in baseline lumen CSA by IVUS did not reach statistical significance. These discordant results between QCA and IVUS may be in part explained in some cases by the presence of eccentric lesions and smaller lumen size than by the size of the IVUS catheter.

Previous IVUS studies showed that late lumen changes, either gain or loss, correlated better with changes in vessel dimension than with plaque progression or regression. Late lumen enlargement of the target lesion as well as non-target lesions with or without stenting may occur under several different conditions. It has been reported that mechanical or chemical injury to media may play a role in positive vessel remodeling of the culprit lesions. On the other hand, it is also possible that some interventional procedures to the target lesion affect the response of the non-target, untreated segments. It has been reported that intracoronary radiation using a gamma source causes positive vessel remodeling of the uninjured reference segments. Several investigators report that endothelial function of the distal reference segments may deteriorate after implantation of first-generation drug-eluting stents. Interestingly, a recent study by Terashima et al reported that this unfavorable effect of first-generation drug-eluting stents on the coronary endothelium may be prevented by the use of an angiotensin-receptor blocker.

Fractional flow reserve (FFR) may help identify significant residual distal stenosis that requires additional intervention. However, FFR only detects significant stenosis at the time of the PCI and does not predict LLG. Moreover, FFR possibly underestimates lesion severity because of transiently impaired microvascular endothelial function distal to chronically occluded lesions.

**Study Limitations**

First, this was a single-center pilot study including a relatively small number of patients. Second, lesions with restenosis or re-occlusion were excluded, so it is uncertain whether the
absence of PHB is related to restenosis or re-occlusion of the target stented lesions. Finally, we did not routinely perform serial IVUS imaging of the distal reference segments in this study population.

In conclusion, the presence of PHB on IVUS predicts chronic enlargement of the coronary segments distal to the stented lesion. This novel finding may help identify lesions that require additional stenting of the distal reference segments immediately after PCI.

Disclosures

Funding: This research received no specific funding. Competing Interests: There are no competing interests for publication. Contribution Statement: All the authors contributed equally with respect to data collection and manuscript preparation.

References