Practical Application of Coronary Imaging Devices in Cardiovascular Intervention

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The significant morbidity and mortality associated with coronary artery disease has spurred the development of intravascular imaging devices to optimize the detection and assessment of coronary lesions and percutaneous coronary interventions. Intravascular ultrasound (IVUS) uses reflected ultrasound waves to quantitatively and qualitatively assess lesions; integrated backscatter and virtual histology IVUS more precisely characterizes plaque composition; angioscopy directly visualizes thrombus and plaque; optical coherence tomography using near-infrared (NIR) light with very high spatial resolution provides more accurate images; and the recently introduced NIR spectroscopy identifies chemical components in coronary artery plaques based on differential light absorption in the NIR spectrum. This article reviews usefulness of these devices and hybrids thereof. (Korean Circ J 2015;45(2):87-95)

KEY WORDS: Coronary artery disease; Diagnostic imaging; Percutaneous coronary intervention.

Introduction

Despite considerable medical advances, coronary artery disease (CAD) remains one of the leading causes of death with a rising global incidence fueled by increasing proportions of elderly individuals and adoption of western-style diets and sedentary lifestyles. The last decades have witnessed meaningful progress in CAD diagnosis and treatment, including the introduction of intravascular imaging modalities to overcome the limited ability of traditional 2-dimensional coronary angiography or “lumenography” to evaluate underlying vessel changes and hidden plaque burden, and its inability to identify plaque characteristics. Preinterventional IVUS imaging identifies lesions at high risk for no-reflow or periprocedural myocardial infarction (MI). Attenuated plaque, defined as hypoechoic plaque with deep ultrasound attenuation without calcification or very dense fibrous plaque, is associated with a higher frequency of no reflow (26.7% vs. 4.6%, p<0.001) and deteriorated post-PCI coronary blood flow (8.0% vs. 2.8%, p=0.001) as compared with non-attenuated plaque. IVUS also allows the detection of calcified plaques which increase the risk of stent underexpansion (71% vs. 14%, p=0.007) and requires additional pre-stent implantation procedures, such as cutting balloon angioplasty or rotational atherectomy to obtain optimal stent expansion. IVUS-guided PCI in the pre-drug-eluting stent (DES) era significantly lowered restenosis and repeat revascularization rates by optimizing stent expansion, with a neutral

Intravascular Ultrasound

Current intravascular ultrasound (IVUS), with 20–45 MHz frequency and 100–200 μm axial resolution, is the most commonly used intravascular imaging modality pre-, during, and post-PCI. grayscale IVUS allows the measurement of lumen, vessel, and plaque areas; qualitative assessment of preinterventional plaque composition; and guidance in stent use optimization. IVUS imaging identifies lesions at high risk for no-reflow or periprocedural myocardial infarction (MI). Attenuated plaque, defined as hypoechogenic plaque with deep ultrasound attenuation without calcification or very dense fibrous plaque, is associated with a higher frequency of no reflow (26.7% vs. 4.6%, p<0.001) and deteriorated post-PCI coronary blood flow (8.0% vs. 2.8%, p=0.001) as compared with non-attenuated plaque. IVUS also allows the detection of calcified plaques which increase the risk of stent underexpansion (71% vs. 14%, p=0.007) and requires additional pre-stent implantation procedures, such as cutting balloon angioplasty or rotational atherectomy to obtain optimal stent expansion. IVUS-guided PCI in the pre-drug-eluting stent (DES) era significantly lowered restenosis and repeat revascularization rates by optimizing stent expansion, with a neutral

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Recent meta-analysis has shown that IVUS-guidance is associated with a lower risk of death, MI, repeat revascularization, and stent thrombosis after DES implantation. It seems that IVUS evaluations of stent underexpansion, malapposition, incomplete lesion coverage, and residual plaque contribute to reduce not only restenosis, but also thrombosis and improve clinical outcomes. However, it is still controversial whether routine IVUS guidance improves clinical outcomes in the DES era (Table 2). IVUS-guided optimization of stent deployment through the determination of stent size, length, and landing zone also improves clinical outcomes regardless of stent type.

While it is difficult to differentiate lipid cores from fibrous tissue

Table 1. Strengths and weaknesses of intravascular imaging devices

| Characteristic                  | IVUS | VH IVUS | Angioscopy | OCT | NIRS |
|--------------------------------|------|---------|------------|-----|------|
| Axial resolution (µm)          | 100  | 200     | 10–50      | 10–15| NA   |
| Assessment of lesion severity  | +    | +       | +          | +   | +    |
| Identification of TCFA         | +++  | +++     | +          | +++ | +    |
| Identification of necrotic core| +    | +       | +          | +   | +    |
| Optimization of stent implantation | +  | +       | +          | +   | +    |
| Evaluation of stent tissue coverage | + | +       | +          | +   | +    |
| Assessment of stent failure    | +    | +       | +          | +   | +    |

IVUS: intravascular ultrasound, VH-IVUS: virtual histology-IVUS, OCT: optical coherence tomography, NIRS: near-infrared spectroscopy, TCFA: thin-cap fibroatheroma

Table 2. Odds ratio for major adverse cardiac events in IVUS-versus angiography-guided PCI

| Study or subgroup | Year | MACE | IVUS | Angiography | Odds ratio | 95% CI |
|------------------|------|------|------|-------------|------------|--------|
|                  |      | Event | Total| Event | Total |        |       |

- **Pre-DES era**
  - RESIST(48) 2000 Death, MI, unstable angina or TLR at 18 months
  - SIPS(50) 2000 Death, MI, TLR at 2 years
  - OPTICUS(51) 2001 Death, MI, CABG, RCR at 12 months
  - TULIP(52) 2003 Death, MI, TLR at 6 months
  - Gaster et al.(55) 2003 Death, MI, any revascularization (median 2.5 years)
  - DIPO(54) 2007 Death, MI, RCR at 6 months
  - AVID(56) 2009 Death, MI, TLR, ST, CABG at 12 months
  - Roy et al.(57) 2008 Death, MI, TVR at 12 months
  - MAIN-COMPARE(58) 2009 Death, MI, TVR at 3 years
  - HOME DES IVUS(59) 2010 Death, MI, RCR at 18 months
  - Claessen et al.(60) 2011 Cardiac death, MI, TVR at 2 years
  - Kim et al.(61) 2011 Death, MI, TLR at 3 years
  - Young et al.(62) 2011 Death, MI, TVR, TLR at 3 years
  - EXCELLENT(63) 2013 Cardiac death, MI, TLR at 12 months
  - Ahn et al.(64) 2013 Cardiac death, MI, TLR, ST at 2 years
  - IRIS-DES(65) 2013 Death, MI, TVR at 2 years
  - Chen et al.(66) 2013 Cardiac death, ST, MI, TVR at 12 months
  - AVIO(67) 2013 Death, MI, TVR at 2 years
  - Hur et al.(68) 2013 Death, MI, TVR, ST at 3 years
  - RESET(69) 2013 Cardiac death, MI, TVR at 12 months
  - ADAPT-DES(70) 2014 Cardiac death, MI, ST at 12 months

- **DES era**
  - MAIN-COMPARE(58) 2009 Death, MI, TVR at 3 years
  - HOME DES IVUS(59) 2010 Death, MI, RCR at 18 months
  - Claessen et al.(60) 2011 Cardiac death, MI, TVR at 2 years
  - Kim et al.(61) 2011 Death, MI, TLR at 3 years
  - Young et al.(62) 2011 Death, MI, TVR, TLR at 3 years
  - EXCELLENT(63) 2013 Cardiac death, MI, TLR at 12 months
  - Ahn et al.(64) 2013 Cardiac death, MI, TLR, ST at 2 years
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  - Chen et al.(66) 2013 Cardiac death, ST, MI, TVR at 12 months
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  - Hur et al.(68) 2013 Death, MI, TVR, ST at 3 years
  - RESET(69) 2013 Cardiac death, MI, TVR at 12 months
  - ADAPT-DES(70) 2014 Cardiac death, MI, ST at 12 months

IVUS: intravascular ultrasound, PCI: percutaneous coronary intervention, MACE: major adverse cardiac event, CI: confidence interval, DES: drug eluting stent, MI: myocardial infarction, TLR: target lesion revascularization, CABG: coronary artery bypass graft, RCR: repeat coronary revascularization, TVR: target vessel revascularization, ST: stent thrombosis

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with grayscale IVUS, integrated backscatter IVUS more precisely defines tissue characteristics by presenting color-coded maps reflecting the structural and biochemical composition of atherosclerotic lesions.\textsuperscript{14} Virtual histology (VH) IVUS also allows a more accurate classification of plaque composition using a spectral analysis of radiofrequency data with electrocardiogram gating as follows: fibrous tissue (dark green), fibrofatty tissue (light green), necrotic core (red), and dense calcium (white).\textsuperscript{15} However, the current classification tree for analysis cannot clearly determine the presence of an intramural thrombus.\textsuperscript{16}

The potential value of VH IVUS-derived plaque types in the prediction of future adverse coronary events was evaluated in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study.\textsuperscript{18} The PROSPECT study was a natural history study of acute coronary syndrome (ACS) patients: all patients underwent PCI for a culprit lesion at baseline, followed by an angiogram and VH IVUS analyses of the three major coronary arteries. Clinical events occurring during the follow-up period were equally attributable to recurrence at the site of the culprit lesion and to nonculprit lesions. Although nonculprit lesions responsible for unanticipated events were frequently angiographically mild, most were characterized by a large plaque burden (≥70%), a small luminal area (≤4.0 mm\textsuperscript{2}), or thin-cap fibroatheromas (TCFA; defined as a lesion fulfilling the following criteria in at least three consecutive frames: necrotic core ≥10% without evident overlying fibrous tissue, and percent atheroma volume ≥40%).

Plaque composition was also associated with the occurrence of distal embolization after PCI. Observational studies showed a clear relationship between the amount of necrotic core and distal embolization and the implied need for adjunctive pharmacological or device-based interventions to reduce the incidence of distal embolizations.\textsuperscript{19–21}

**Angioscopy**

Angioscopy consists of a specially designed fiberscope for coronary use and enables macroscopic pathological diagnosis of cardiovascular diseases from the inside.\textsuperscript{22} Angioscopy is a useful tool to detect thrombi and distinguish between the content of the thrombi (platelet- or fibrin-rich) based on their color (white or red). It can also be used to detect vulnerable plaque. A normal coronary artery appears as glistening white, whereas atherosclerotic plaque can be categorized as yellow or white.\textsuperscript{23} Thus, a higher yellow color intensity likely represents the lipid pool underneath a thin-fibrous cap. Currently, percutaneous angioscopy is mainly used to evaluate the stabilization and regression of vulnerable plaques by medical, interventional, and surgical therapies. It is also useful in visualizing vulnerable stents: a lack of endothelization and stent malapposition can both be detected with this modality.\textsuperscript{24,25} However, the histological and molecular changes inside the plaque cannot be evaluated because angioscopic observation is limited to surface color and morphology. Also, quantitative assessment of color, distance, and volume is difficult.

**Optical Coherence Tomography**

Optical coherence tomography (OCT) is a catheter-based technology that provides high-resolution cross-sectional tissue images from backscattered infrared light with an axial resolution of 12–15 μm, 10 times higher than that of IVUS.\textsuperscript{26} Despite providing in vivo images with better histological detail, the broad use of time-domain (TD) OCT has been hampered because it requires the inflation of a proximally placed balloon. The introduction of Fourier-domain (FD) OCT with a much faster frame rate and pullback speed than TD OCT has allowed for faster image acquisition with high-rate saline infusion and without proximal occlusion.\textsuperscript{27} Although the penetration of OCT is lower than that of IVUS, it affords a better evaluation of vulnerable plaque by providing a detailed image of the endoluminal borders, a higher detection rate of lipid core, measurement of fibrous cap, and macrophage detection. In comparative evaluation of culprit lesions in patients with acute MIs, OCT was more sensitive in detecting plaque rupture, plaque erosion, and TCFA (lipidic plaque with cap thickness <65 μm) than IVUS or coronary angioscopy.\textsuperscript{28} Because the resolution power of OCT is 10 times higher than that of IVUS, OCT is able to better delineate the lumen-vessel boundary. In the OPUS-CLASS study, both minimum lumen diameter and the area measured by IVUS were significantly greater than those measured by FD-OCT.\textsuperscript{29,30} underscoring that IVUS overestimates lumen area and has less reproducibility than FD-OCT, which provides accurate and reproducible quantitative measurements of coronary dimensions and more efficiently assesses functional stenosis severity, particularly in small vessels (Table 3).

In the evaluation of lesion morphology after stent implantation, OCT allows more frequent visualization than IVUS of stent features, including inadequate stent apposition (ISA), tissue protrusion, thrombus, and stent edge dissection.\textsuperscript{31} Gutiérrez-Chico et al.\textsuperscript{32} reported that maximal ISA distances <270 μm after stent implantation showed resolved ISA at follow-up, whereas maximal ISA distances ≥850 μm were associated with persistent ISA.\textsuperscript{33} A recent study by Im et al.\textsuperscript{34} demonstrated the following risk factors for specific conditions: 1) acute ISA: baseline diameter stenosis >70%, calcified lesion, and stent length >25 mm, 2) late-persistent ISA: acute ISA volume and acute ISA within stent edges, and 3) late-acquired ISA: plaque/thrombus prolapse after stent implantation.

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Table 3. OCT-derived anatomical criteria for defining functional severity

| Author          | No. of lesions | Diagnosis                | % DS | FFR | Functional significance | Cutoff | AUC | Diagnostic accuracy (%) |
|-----------------|----------------|--------------------------|------|-----|-------------------------|--------|-----|-------------------------|
| Shiono et al.30  | 62             | Stable angina (39.3%)    | 58±17| 0.72±0.14 | FFR <0.75          | MLD: 1.35 mm | MLD: 0.917 | MLD: 85.5 |
|                 |                | Asymptomatic control (25.0%) |     |     |                         | MLD: 1.91 mm | MLD: 0.904 | MLD: 85.4 |
|                 |                |                          |      |     |                         | AS: 70% | AS: 0.940 | AS: 90.3 |
| Gonzalo et al.26 | 61             | Stable angina (39.3%)    | 512±8| 0.80±0.11 | FFR ≤0.80       | MLD: 1.34 mm | MLD: 0.73 | MLD: 73   |
|                 |                | Asymptomatic control (25.0%) |     |     |                         | MLD: 1.95 mm² | MLD: 0.74 | MLD: 72   |
|                 |                |                          |      |     |                         | AS: 70% | AS: 0.61 | AS: 57    |
| Pyxaras et al.71 | 55             | Stable angina (78%)      | 34±12| 0.85±0.10 | FFR ≤0.80       | MLD: 1.59 mm | MLD: 0.80 | MLD: 79   |
|                 |                |                          |      |     |                         | MLD: 2.88 mm² | MLD: 0.78 | MLD: 72   |
| Pawlowski et al.71 | 71            | Stable angina (100%)     | 50±8 | 0.72±0.08 | FFR <0.80      | MLD: 1.28 mm | MLD: 0.90 | MLD: 87   |
|                 |                |                          |      |     |                         | MLD: 2.05 mm² | MLD: 0.91 | MLD: 87   |
| Shiono et al.71  | 62             | Stable angina (100%)     | 52±9 | 0.79±0.13 | FFR ≤0.80     | MLD: 1.31 mm | MLD: 0.816 | MLD: 80.7 |
|                 |                |                          |      |     |                         | MLD: 1.59 mm² | MLD: 0.813 | MLD: 77.4 |
|                 |                |                          |      |     |                         | AS: 70% | AS: 0.807 | AS: 72.4 |

OCT: optical coherence tomography, DS: diameter stenosis, FFR: fractional flow reserve, AUC: area under the curve, MLD: minimal lumen diameter, MLA: minimal lumen area, AS: area stenosis

Owing to its greater spatial resolution, OCT also effectively assesses neointimal healing and restenosis patterns within stented segments. Late in-stent restenosis (ISR occurring after 1 year) was documented by OCT to have heterogeneous neointima and a significantly higher incidence of lipid-rich neointima, TCFA-like neointima, microchannels within neointima, and neointimal disruption compared with early ISR.34 The latter atherosclerotic neointimal degenerative changes might underlie the clinical instability of late ISR.34 Vergallo et al.35 reported that stents with greater neointimal hyperplasia were more frequently associated with features of vulnerability regardless of the stent type and time from implantation.

Optical coherence tomography also might be a useful tool in PCI optimization.39 In a study by Prati et al.35 angiographic plus OCT guidance compared with angiographic guidance alone led to additional interventions (repeat balloon inflation or additional stenting) in 34.7% of cases, in association with a significantly lower risk of cardiac death or MI during a 1-year follow-up period. On the other hand, Habara et al.36 reported that FD-OCT guidance was associated with smaller stent expansion and more frequent significant residual reference segment stenosis compared with IVUS guidance, suggesting a significant advantage for IVUS over OCT. In contrast, two university centers (Keimyung University and Ulsan University) evaluated clinical outcomes after a 1-year follow-up period after IVUS- or OCT-guided PCI, and the two strategies showed a similar incidence of MACE (cardiac death, MI, and target lesion revascularization; 3.9% vs. 4.0%, respectively, p = not significant (NS)) or definite/probable stent thrombosis (0.8% vs. 1.2%, respectively, p = NS), suggesting that OCT guidance is a possible alternative strategy for stent optimization (Fig. 1).40 OCT guidance can also guide intervention to avoid balloon angioplasty (POBA) and stenting in specific lesion subset. In a study by Cervinka et al.40 OCT showed clear differentiation between real lesions and thrombus formation in the setting of ST segment elevation MI and led to the avoidance of POBA and stenting. However, the OCT criteria to guide PCI and long-term clinical follow-up of OCT-guided PCI remain undefined; further studies are warranted to clarify the role of OCT in PCI guidance or optimization.

Even though OCT enables the accurate assessment of plaque types, stent strut positioning, and endothelization due to its better spatial resolution and faster data acquisition, its low axial penetration does not provide optimal visualization of the arterial wall. It also requires the injection of contrast during image acquisition, and therefore it cannot be performed in situations where there is no coronary flow, such as in complete occlusion.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is based on light absorbance by organic molecules while scanning an artery through blood and during cardiac motion. The reflectance spectra from wavelengths between 400 nm and 2400 nm enable an analysis of the chemical composition of biological tissue. The goal of intracoronary NIRS is to provide a “chemogram” of the arterial wall to find lipid core plaque using optical spectroscopy and spatial resolution. OCT is a promising modality to improve the differentiation between real lesions and thrombus formation in the setting of ST segment elevation MI, as well as for guiding PCI in specific lesion subsets.
LCP detection in human coronary autopsy specimens was validated by the SPECTroscopic Assessment of Coronary Lipid trial. Madder et al. evaluated the frequency of LCP according to clinical presentation. The target lesions responsible for ACS were frequently composed of LCP, and LCPs were often found in remote, nontarget areas. As expected, both target and remote LCPs were more common in patients with ACS than in those with stable angina. Stent implantation in LCP-containing lesions can result in adverse angiographic and clinical outcomes, including no-reflow, distal embolization, and periprocedural MI. In addition to advanced atherosclerosis, NIRS helped to detect higher lipid content in early CAD with endothelial dysfunction, which may be closely associated with a rapid progression of coronary atherosclerosis and future cardiovascular events due to plaque rupture. Dixon et al. used NIRS to guide stent length selection and optimal lesion coverage. This finding suggested that the use of NIRS combined with conventional coronary angiography could avoid incomplete lesion coverage or possible placement of the stent ends within a LCP, which could result in adverse angiographic and clinical outcomes, including no-reflow, distal embolizations, and periprocedural MIs. Although information

Fig. 1. OCT-guided PCI. A 63-year-old man was diagnosed with non-ST segment elevation myocardial infarction. A: baseline coronary angiogram showed significant stenosis of the proximal left circumflex artery. Pre-interventional OCT revealed a minimal lumen area of 1.93 mm² and red thrombi (red arrow). The minimal lumen diameters at the proximal and distal reference segments were 2.69 mm and 2.67 mm, respectively, and the lesion length was 16.9 mm. B: a coronary angiogram after biolimus-eluting stent (2.75×18 mm) implantation. Post-interventional OCT showed a minimal lumen area of 6.77 mm² and a thrombic protrusion (blue arrow). OCT: optical coherence tomography, PCI: percutaneous coronary intervention, MLA: minimal lumen area, MSA: minimal stent area.
about the chemical composition may contribute to early identification of high-risk plaque, a potential limitation may be its inability to assess the depth of a lipid core and its measurement of lipid volume has not been validated so far. Therefore, this weakness can be overcome by its use in combination with other imaging modalities such as IVUS or OCT.

**Hybrid Intravascular Imaging**

By combining different imaging modalities to overcome the innate limitations of each, hybrid imaging allows for a more detailed and comprehensive coronary artery evaluation. Hybrid coronary biplane angiography and IVUS provides information on vessel geometry through angiography and vessel wall pathology via IVUS. Three-dimensional models allow a comprehensive understanding of vessel geometry and plaque distribution and have been extensively used research tools to evaluate the association between local hemodynamic factors and plaque progression. The combination of angiography and OCT can provide detailed information regarding vessel geometry and plaque type, which may contribute to the identification of vulnerable or ruptured plaques and thus, the effect of blood flow on atherosclerotic evolution.

Hybrid IVUS and NIRS imaging provides insight on plaque composition and lesion architecture. The recently introduced true vessel characterization Imaging System (MC 7 system, InfraReDx, Burlington, MA, USA) allows the simultaneous assessment of plaque composition both in terms of its chemical and morphologic characteristics. It can be an alternative approach to assess the vulnerability of ostial coronary lesions not reachable by OCT.

The combination of IVUS and OCT may provide an optimal assessment of the volumetric and structural characteristics of a coronary artery. Combining both modalities allows for a more accurate detection of high-risk plaques and would be useful in planning and assessing the outcome of PCI. The correct stent diameter could

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**Fig. 2.** Angiographic and NIRS findings in acute STEMI. A 56-year-old patient with acute chest pain and inferior-posterior injury was referred for primary PCI (A). Angiography of the right coronary artery revealed complete occlusion (B). Aspiration yielded a thrombus characteristic of STEMI (C) and resulted in a TIMI flow grade 3 (D). NIRS performed after the TIMI flow grade 3 was established revealed a prominent, nearly circumferential lipid core plaque concentrated at the culprit site (E). NIRS: near-infrared spectroscopy, STEMI: ST segment elevation myocardial infarction, PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction. Adopted from Madder RD, Goldstein JA, Madden SP, et al. JACC Cardiovasc Interv 2013;6:838-46. 74
be selected through the use of IVUS while a detailed evaluation of the final result and procedural complications could be obtained with OCT.

Conclusion

The ideal intravascular imaging device should enable both a rapid and an accurate assessment of the coronary arteries while providing sufficient information on local and systemic atherosclerosis-related factors. Grayscale IVUS is routinely used in daily practice. Although it provides information before, during, and after PCI, it has poor resolution and omits plaque composition. The introduction of OCT has addressed the resolution limitation, and various modalities including VH IVUS, OCT, angioscopy and NIRS are currently in use to provide information about plaque composition, such as plaque vulnerability. Hybrid intravascular imaging devices also provide better and more tailored data regarding PCI. More reliable and accurate imaging with further technological advances will allow for better understanding and treatment of CAD in the future.

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