Angioscopic Findings after Drug-Eluting Stent Implantation

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Abstract
In-stent restenosis is the Achilles' heel of standard or bare-metal stent (BMS) implantation, occurring in 10–40% of the patients. Drug-eluting stent (DES) are supposed to inhibit inflammation and neointimal growth and, subsequently, in-stent restenosis. The neointimal proliferation inside the stent is recognized as lumen late loss on angiograms or as an obstruction area (or volume) on intravascular ultrasound (IVUS) in chronic phase. Coronary angioscopy provides direct visualization of the lumen and is capable of macroscopic pathologic diagnosis of atherosclerotic plaques and intracoronary thrombi. This modality is also able to supply detailed information on stent coverage with neointimal hyperplasia. The neointimal growth inside the stent is evaluated as white neointimal coverage over the stent struts. Angioscopic view inside the DES is quite different from that inside the BMS. In this article, the difference in angioscopic findings between the DES and the BMS is shown.

Introduction
The major limiting factor of balloon angioplasty is the occurrence of restenosis in about 30–60% of patients, depending on patients' and lesion characteristics, and technical aspects of the coronary intervention [1]. Restenosis is characterized by a three-stage response of vessel injury result from balloon dilatation: (1) acute elastic recoil, (2) chronic elastic recoil (negative remodeling), and (3) neointimal proliferation [2]. The first effective strategy to lower the restenosis rate has been implantation of bare-metal stents (BMS) [3, 4]. BMS implantation has resulted in a decline of the restenosis rate to 10–40% by elimination of acute and chronic elastic recoil [5, 6]. However, in-stent restenosis, mainly due to neointimal proliferation, remains the major limiting factor of percutaneous coronary intervention (PCI). The pathologic process of in-stent restenosis is characterized by an inflammatory healing response after stretch and damage of the vessel wall [7–9]. Initially, platelets are activated and attach around the stent struts followed by adhesion of inflammatory cells. Several kinds of cytokines and growth factors are released, leading to smooth muscle cell migration and proliferation. The smooth muscle cells are replaced by extracellular matrix at 3–6 months after stent implantation [10, 11].

In recent years, the combination of stent properties to inhibit recoil with drugs that inhibit the neointimal proliferation, utilizing the stent as a local delivery platform, has been developed as a highly promising prevention from in-stent restenosis. In general, the drug-eluting stent (DES) consists of three major components: (1) the drug, (2) the polymer coating, and (3) the stent. The most widespread drug, sirolimus (rapamycin), regulates protein translation, resulting in a G1 arrest of the cell cycle and inhibition of
vascular smooth muscle cell migration, proliferation and growth [12]. Sirolimus is also a strong inhibitor of inflammation without cellular toxicity in low doses. Clinical studies that have addressed sirolimus-eluting stent (SES) are: RAVEL [13], SIRIUS [14], E-SIRIUS [15], and C-SIRIUS [16]. Currently, the SES is being investigated in all types of lesions and patients in clinical studies and registries, such as restenotic lesions [17], bifurcation lesions, diabetics [18], acute coronary syndrome [19] and multivessel disease. According to current evidence, the SES is generally more effective to prevent restenosis and to reduce target lesion revascularization than the BMS. Thin layer of the inhibited neointimal growth after the SES implantation is recognized as minimal late lumen loss on angiograms [13, 14] and nearly abolished percent area (or volume) obstruction on intravascular ultrasound (IVUS) [17, 20].

**Coronary Angioscopy**

Coronary angioscopy has been approved for clinical use in Japan. Therefore, this imaging modality is often utilized for PCI and for follow-up studies. The system of angioscopy consists of an imaging catheter, a light source, a color television camera and monitor, and a videotape recorder. The light source employed is a high-intensity (300 W) xenon light. Two types of angioscopic catheters are available; one is an occlusion type and another type is maintenance of coronary blood flow. It is required to remove the blood from the viewing field and to displace the blood with transparent fluid in order to acquire clear angioscopic images. We commonly use the occlusion-type angioscopic catheter (VecMova Neo®, FiberTech Co., Chiba, Japan) because it can obtain continuous images of the whole vessel wall. This catheter is 4.5-French, rapid-exchanged type and is composed of two elements (image bundle in delivery catheter). A guide catheter > 6 French in diameter is needed for angioscopic procedure. The image bundle consists of 3,000 optical fibers with microlens at the distal tip, which can be advanced 7 cm in front of the delivery catheter along a 0.014-inch guide wire. A compliant occlusion balloon is located at the distal tip of the delivery catheter and the balloon is inflated manually during image acquisition. Warmed physiological saline (or Ringer’s lactate) is continuously irrigated through the delivery catheter at a rate of 0.5–1.0 ml/s by a power injector. Prior to observation, the white balance is adjusted for color correction. Light power is also adjusted to avoid reflection and to obtain images with adequate brightness for determination of the color [21, 22].

Angioscopy provides direct visualization, that is, high-resolution, three-dimensional, full color images of the coronary lumen. The image of angioscopy is applicable for macroscopic pathohistological diagnosis of intracoronary structures, such as atherosclerotic plaque, thrombus, and neointimal hyperplasia within the segment that had undergone past PCI based on the surface color and morphology. Coronary plaque is presented as a nonmobile, elevated, and/or protruding structure that can be clearly demarcated from the adjacent vessel wall. The plaque is classified white or yellow based on the color. In addition, its yellow grade is classified semiquantitatively as 0: white, 1: light yellow, 2: yellow, or 3: dark yellow (Figure 1) [22]. According to the morphology, the plaque is divided into stable plaque, which has a smooth surface, or into complex plaque, which has an irregular surface. The complex plaque includes ruptured plaque, eroded plaque, intimal flap, fissure, and ulceration. Thrombus is presented as a coalescent red, white, mixed (white and red), or pinkish-white superficial, intraluminal, or protruding mass adherent to the vessel surface but clearly a separate structure that persisted despite being flush with a saline (or Ringer’s lactate) solution (Figure 1) [23, 24]. Disrupted yellow plaque and thrombus are found not only in the culprit lesion of acute coronary syndrome but also in the nonculprit lesion [24–26]. Stable white plaque without thrombus is often seen in the ischemia-related lesion of stable patients [27].

Although protruding thrombus and complex plaque remain after balloon angioplasty, the stent struts compressed the plaque and thrombus and the coronary lumen is maintained sufficiently immediately after stent implantation [21]. The stent struts overlying the plaque and/or thrombus are usually seen (Figure 2). In rare cases, the plaque and/or thrombus protrude into the lumen from the space between the stent struts. There are some limitations