Curr Cardiovasc Imaging Rep (2016) 9: 5
DOI 10.1007/s12410-015-9367-4

Angioscopy in 2015: the Role of Macroscopic Pathology in Living Patients

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Published online: 16 January 2016

Abstract Angioscopy can detect lipid-rich yellow plaques that are regarded as vulnerable plaques. The patients who have multiple yellow plaques are regarded as vulnerable patients. The disrupted plaques can also be visualized directly by angioscopy, but they can be detected more sensitively as the presence of thrombus. On the other hand, angioscopy can also evaluate the neointima formed over stents. The follow-up angioscopic examinations after the implantation of coronary stents visualized atherosclerosis progression as the formation of yellow plaque in the stent-implanted segments. Recently, the presence of yellow plaque at 1 year after stent implantation has been demonstrated to be the risk of future stent failure. Atherosclerosis progression shown by the formation of yellow plaque may be the major mechanism and "final common pathway" for the very-late stent failure.

Keywords Angioscopy · Yellow plaque · Thrombus · Neointima · Neoatherosclerosis · Very-late DES failure

Introduction

Angioscopy can directly visualize the intra-coronary luminal condition, giving us the information of macroscopic pathology, in the patients alive. Lipid-rich atherosclerotic plaques are detected as yellow plaques, and their yellow color intensity (grade 0–3) has been demonstrated as a marker of plaque vulnerability [1]. Yellow color grade is negatively correlated with fibrous-cap thickness [2], and grade 3 yellow plaques are compatible with thin-cap fibroatheroma (TCFA). The yellow plaques of higher yellow color grade are known to have higher prevalence of plaque disruption [1]. The disruption of plaques, including both plaque rupture and plaque erosion, can be detected by the presence of thrombus even if the rupture itself cannot be visualized directly. Angioscopy is regarded as the most sensitive intracoronary imaging device to detect thrombus. Furthermore, the patients with multiple coronary yellow plaques are known to be vulnerable patients who have higher incidence of future coronary event [3••]. Therefore, angioscopy is one of the best intracoronary imaging devices to detect disrupted plaques, vulnerable plaques, and vulnerable patients. Angioscopy is a very simple device that makes it possible to see coronary lumen directly by our eyes; however, the device itself is still mechanically immature and needs improvement.

New Angioscopic Findings in a Recent Few Years

In a recent few years, according to the emergence of new second-generation drug-eluting stents (DES), their conditions at follow-up have been reported in addition to the long-term follow-up reports on the first-generation DES by various investigators. Furthermore, there were some reports on the angioscopic examinations of other vessels, i.e., femoral artery, pulmonary artery [4], and aorta [5, 6••].

First generation DES has been reported to have poor neointima coverage and high incidence of thrombus formation [7]. Furthermore, Cypher sirolimus-eluting stents (SES) has been reported to accelerate the progression of atherosclerosis as shown by the formation of yellow plaque [8••]. In the first-

This article is part of the Topical Collection on *Intravascular Imaging*

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generation DES, the better neointima coverage was associated with the better vasomotor response against acetylcholine in the coronary segment distal to the stent [9, 10]. As peri-stent contrast staining (PSS) has been recognized as a predictor of late stent thrombosis, angioscopy revealed worse neointima coverage with higher incidence of yellow plaque and thombus at the site with PSS than at the site without PSS [11].

Xience or Promus everolimus-eluting stents (EES) as one of the second generation DES had similarly poor or slightly better neointima coverage than Cypher SES, but had less thrombus and less yellow plaque than Cypher SES at 7–8 months follow-up [12, 13]. Endeavor zotarolimus-eluting stent (ZES), which is also one of the second generation DES, at 4 months already had good neointima coverage with low incidence of thrombus as those at 8 months, although the yellow plaque was detected more frequently at 4 months than at 8 months [14]. The yellow color decreased significantly from baseline to 1-year follow-up in Endeavor ZES but it did not change in Xience EES while the incidence of thrombus decreased significantly in both stents to a very low level [15]. This finding suggests that neointima coverage would be good in both stents but that the sealing effect by a thick fibrous neointima may be expected only in Endeavor ZES.

The results of DESNOTE study were recently reported [16••]. This study has demonstrated that the presence of yellow plaque in the stent-implanted segment at 1-year follow-up is associated with the future event of DES failure including cardiac death, acute myocardial infarction or unstable angina associated with the stent, or need for revascularization associated with the stent. Multivariable analysis revealed the presence of yellow plaque (hazard ratio [HR] 5.38; $p = 0.02$) and absence of statin therapy (HR 3.25; $p = 0.02$) as risks of very-late DES failure. These findings suggest that the progression of yellow plaque would be a major mechanism of very-late DES failure and statin treatment or probably other anti-atherosclerotic treatment may be able to reduce the events.

There were also some studies reported on the atherosclerosis in the native coronary artery. The prediabetic patients as well as the diabetic patients were associated with a larger number of coronary yellow plaques than the nondiabetic patients, suggesting that the early-stage diabetes is already a risk of coronary disease [17]. The extremely elevated blood

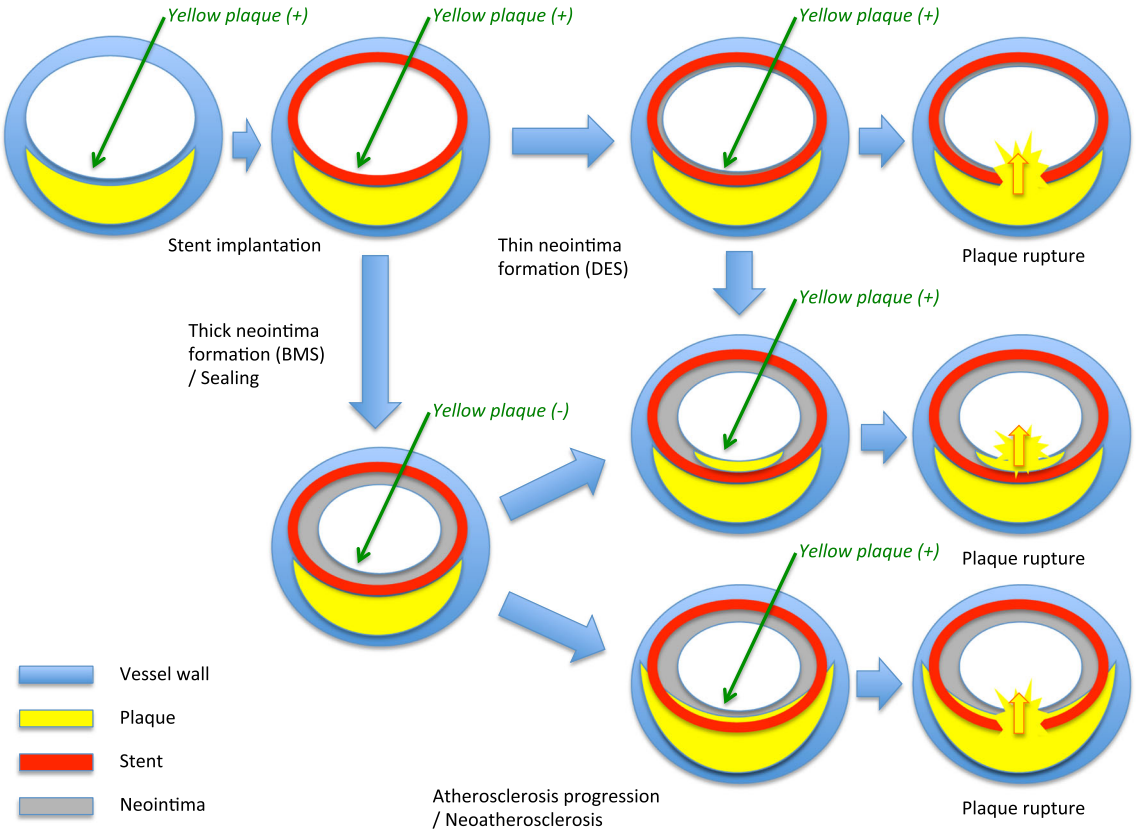

Fig. 1 The process of atherosclerosis progression after stent implantation from the angioscopic viewpoint. Stent is often implanted over yellow vulnerable plaques. However, if BMS or Endeavor stent is implanted, a thick fibrous non-atherosclerotic white neointima covers and seals the plaque and makes the lesion white and stable. It usually takes 5–10 years for the white thick neointima to have yellow vulnerable plaques again by the progression of atherosclerosis. The progression of atherosclerosis may occur as the formation of a new plaque inside the neointima or as the expansion of the pre-existing underlying plaque. On the other hand, if other DES is implanted, very thin neointima is usually formed over the stent and the lesions remain yellow. The rupture of those yellow plaques may cause very-late stent failure, i.e., stent thrombosis or restenosis, relatively soon

thrombogenicity had been reported in the patients with acute myocardial infarction; however, the presence of silent plaque rupture with thrombogenesis was not associated with elevated blood thrombogenicity [18], suggesting that the elevated blood thrombogenicity should not be a mere result of intracoronary thrombogenesis but may be a cause of acute myocardial infarction onset. Plaque stabilization as shown by the reduction of yellow color by statin treatment had been reported previously as the results of TWINS study [19], and its subanalysis clarified that the reduction of yellow color was delayed in the diabetic patients than in non-diabetic patients [20]. The presence of yellow plaque and ruptured plaque at the target lesion of PCI were associated with the occurrence of plaque debris distal embolization demonstrated by filter-type distal protection device [21].

Although the paclitaxel-coated nitinol drug-eluting stent (Zilver PTX) and BMS implanted in the femoral artery had different degree of neointima coverage at a few months, both similarly had high incidence (79–80 %) of yellow plaque and thrombus [22], which might explain the clinical outcomes of those stents.

Angioscopic Viewpoint on Neoatherosclerosis and Very-Late Stent Failure

In the DESNOTE study [16••], the presence of yellow plaque at 1 year after DES implantation has been demonstrated as a risk of future stent failure, suggesting that atherosclerosis progression, i.e., the formation of yellow plaque, may be a major mechanism and "final common pathway" for the very-late stent failure including both stent thrombosis and restenosis [23]. Therefore, it is quite reasonable that the absence of statin therapy was also demonstrated as a risk of very-late stent failure in DESNOTE study, as the statin treatment had been demonstrated to reduce the yellow color grade of yellow plaques in TWINS study [19]. After the implantation of BMS, it usually takes 5–10 years for the stent-implanted site to cause ACS event again, in which disrupted yellow plaque is usually detected at the culprit. This would be explained by an angioscopic finding that BMS is usually covered and sealed by a thick fibrous white neointima (Fig. 1), requiring 5–10 years for a new yellow plaque to be formed in the thick white neointima and cause event by its disruption. On the other hand, in general, very thin neointima is usually formed over DES (excluding Endeavor ZES) and the yellow plaque under the stent remains yellow [15], suggesting that only a few years would be required for the pre-existing yellow plaque to cause event by its disruption.

Because the cause of ischemic coronary events including stable angina, unstable angina, and acute myocardial infarction is the formation and disruption of lipid-rich vulnerable plaques both in the native coronary artery and in the stent-implanted coronary artery, the way to prevent them is to prevent the progression of atherosclerosis or to form a thick fibrous-cap on the vulnerable plaques. The former would be achieved by the optimal medical therapy, and the latter would be achieved by statin therapy or by the implantation of BMS, Endeavor ZES, or bioresorbable scaffold. Although the angioscopic observation of the bioresorbable scaffold has not been reported yet, OCT data has suggested the formation of thick fibrous neointima.

Conclusions

Angioscopy can directly visualize the intracoronary image, especially yellow plaques and thrombus. Yellow plaques are vulnerable plaques that cause coronary events both in the native coronary arteries and in the coronary segments after stent implantation. Therefore, the reduction of yellow color may be able to prevent both acute coronary syndrome and very-late stent failure. The target of angioscopic observation is now expanding from coronary artery to femoral artery, pulmonary artery, and to aorta. Direct observations of those arteries before and after local or systemic treatments may clarify the natural process of diseases and the effect of those treatments.

Compliance with Ethical Standards

Conflict of Interest Yasunori Ueda reports personal fees from Abbott Vascular Japan, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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