Coronary Artery Discoveries Made Using Direct Angioscopic Visualization: Fifteen Years of Experience and Further Expectations

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The most distinctive feature of coronary angioscopy is its ability to directly visualize the vessel. This allows direct observation of plaque natural history, including progression, rupture, and subsequent thrombus formation, in living patients. To date, coronary angioscopy has resulted in numerous discoveries, and we expect to find additional new phenomena using this technique. We introduced coronary angioscopy in 2002 and observed many surprising things. These included our observations of old saphenous vein grafts wherein dense, yellow plaques with numerous thrombi were observed in normal lesions. During the drug-eluting stent era, the healing process was observed to be absolutely different than after bare metal stent implantation. Following bare metal stent implantation, the stented site was covered with thick, white, smooth neointima; after implanting a first-generation drug-eluting stent, neointima formation was poor and the neointima was yellow, in some cases. This phenomenon, now called "neoatherosclerosis" was first observed using angioscopy. The cause of the yellow plaque formation was proven to be due to inflammation caused by the poor biocompatibility of the stent polymer. Developments in drug-eluting stent technology were clearly observed using angioscopy. Adequate healing after the implantation of second-generation drug-eluting stents was observed in stable coronary stenotic lesions; however, inadequate healing was observed in vulnerable lesions. Additional new technologies will be required to heal vulnerable lesions. In the near future, biodegradable vascular scaffolding will be available. Angioscopic observation of the healing process will be important to assess the safety of this new technology. Optical coherence tomography can also be used to observe and measure neointimal thickness after drug-eluting stent implantation. However, the layered thrombi attached to vessel walls cannot be assessed using this technology; angioscopy can clearly detect these thrombi. The hazy angiographic appearance of the lotus-root structures, sometimes seen using optical coherence tomography, were thought to be recanalized channels that formed after thrombosis. Angioscopy clearly showed these lotus-root observations to be due to fibrin nets. The characteristics of plaques, after stent implantation involving tissue protrusion, were also unclear; however, angioscopy identified the exact tissue characteristics and allowed the suggestion of further therapies. Recently, the angioscopic observation of the aorta has been a focus. Various thrombi and plaques may be observed on the surface of the aorta. Understanding these structures may elucidate the mechanism of acute aortic syndrome. Angioscopy is the only tool that allows the direct observation of the intravascular world and has a high potential for allowing new discoveries in living people.

Key words: angioscopy, saphenous vein graft, drug-eluting stent, neoatherosclerosis

Introduction

What makes the use of angioscopy so attractive? The most distinctive feature of coronary angioscopy is its ability to directly visualize the coronary artery; seeing is believing. Many coronary artery happenings are only able to be observed using angioscopy. Angioscopy is the only tool that allows the direct observation of plaque natural history, including its progression, sometimes its regression, and finally its rupture and the subsequent thrombus formation, in living patients. To date, coronary...
Angioscopy has allowed many new discoveries and we expect to discover additional new phenomena using this technique. Our institute introduced coronary angioscopy in 2002, and its use has allowed us to observe many surprising things. In this review, we describe angioscopic findings that cannot be detected using other modalities.

**Old Saphenous Vein Grafts**

Saphenous veins are an important source of coronary arteries for aorta bypass grafting. After grafting, arterialization of a saphenous vein graft (SVG) is thought to accelerate atherosclerosis. Indeed, the 10-year patency rate for SVGs is less than 60%.\(^1\) To understand the precise mechanism of SVG degeneration, angioscopic observations were performed using old SVGs. Surprisingly, dense yellow plaques and various thrombi were angiographically observed throughout normal lesions (Fig. 1).\(^2\) This phenomenon was also detected using optical coherence tomography (OCT).\(^3\) In an attempt to understand this phenomenon, we analyzed the factors affecting SVG degeneration. Thrombi and plaques were semiquantitatively assessed and compared with coronary risk factors and laboratory data. Positive relationships were found with the number of risk factors that patients had, as well as with their glycosylated hemoglobin (HbA1c) values.\(^6\) This study indicated that controlling conventional coronary risk factors, especially diabetes mellitus, were important for maintaining SVG patency. We also observed SVG stenosis during percutaneous coronary intervention (PCI). If angioscopy of SVGs demonstrated white plaques and there were no thrombi visible, a standard PCI strategy seemed to be appropriate. However, if the SVG plaque was yellow and was associated with thrombi, PCI was recommended to be performed carefully.\(^5\) First, thrombus aspiration was recommended to be performed before balloon dilatation. Then, distal protection was used to prevent distal embolisms. We previously reported the usefulness of self-expandable stents in association with degenerated SVGs.\(^6\) This strategy reduced the rate of distal embolism complications; unfortunately, self-expandable stents are no longer available.

**Stent Observations**

**Bare metal stents**

Angioscopy has played an important role in understanding plaque healing after stent implantation. Since the bare metal stent (BMS) era, our institute has studied the post-stenting healing process. Chronic follow-up angioscopy, after PCIs involving the implantation of BMSs, revealed that thick, white, smooth neointima, without thrombi, fully covered the stent struts; the struts were not visible even after an acute coronary syndrome (ACS) event involving complex yellow plaque and thrombi in the culprit lesion. Therefore, this phenomenon was understood to yield plaque sealing and stabilization.\(^7\) As mentioned previously, BMS segments avoid the development of in-stent restenosis (ISR) were considered to demonstrate favorable healing within a couple of years. According to long-term angioscopic follow-up examinations, the neointima became thinner and increasingly transparent within 3 years after BMS implantation.\(^8\) Angiographic observations sometimes indicated that the minimum luminal diameter, at the BMS implantation site, also became slightly dilated compared with the 6-month follow-up examination. This phenomenon was thought to be identical to the angioscopic observation of thin neointima formation.

**First generation drug-eluting stents (1st-G DES)**

In the DES era, angioscopic studies have been more important for helping to understand the post-DES implantation healing process. To overcome ISR, DESs were developed, including sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs). Since their introduction, these two DES types have been

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Fig. 1 Angioscopic images of angiographically normal old saphenous vein grafts. (A, B and G) show glittering yellow and fragile plaques. Some of them are broken and may travel away from their site of origin. Others reveal yellow plaque and thrombi (red, white, and mixed thrombi of various shapes). (E and H) show markedly red thrombi.\(^5\)
widely used. However, an unanticipated new problem arose with DES use; late stent thrombosis (LST) and very late stent thrombosis (VLST). Angioscopy contributed to the identification of many aspects of the mechanisms associated with LST and VLST development. Kotani et al. demonstrated that neointimal coverage, after SES implantation, was poor, compared with that associated with BMSs. Neointimal coverage was clearly defined by angioscopic findings. In this paper, neointimal coverage was determined by 4 grading system; Grade 0 was defined as stent struts that were fully visible, similar to immediately after implantation. Grade 1 was defined as stent struts that bulged into the lumen and although covered, were still transparently visible. Grade 2 was defined as stent struts that were visible, but not clearly seen. Grade 3 was defined as stent struts that were not visible by angioscopy. This grading system has been used in numerous angioscopic investigations. Many reports have described the poor and delayed neointima formation after 1st-G DES implantation. Poor neointimal coverage, after 1st-G DES implantation, is thought to be one of the mechanisms contributing to LST and VLST. This phenomenon was observed to continue for up to 2 years. So, a consideration of the need for continued dual anti-platelet therapy seems to be important. Another mechanism resulting in LST and VLST was neoatherosclerosis. This plaque healing concept was first reported following angioscopic observations. After the introduction of the 1st-G DESs, the DES effects on plaque stabilization were expected to be similar to those associated with BMSs; however, plaque healing following implantation of 1st-G DESs was completely different. In 2006, we reported the formation of yellow neointima 3 months after SES implantation. In that study, we clearly demonstrated that the frequency of yellow plaque increased 3 months after stenting (Fig. 2). Some cases developed this newly formed, yellow neointima that is now called neoatherosclerosis. Further, some cases also demonstrated increased atheroma volumes that even-

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tually ruptured, resulting in ACS, which is another mechanism of VLST development. Figure 3 demonstrates a case of VLST associated with SES-induced yellow intima. A 43-year-old man, with a history of stable angina pectoris, underwent elective PCI, involving SES implantation into his left circumflex artery. Immediately after PCI, the plaque under the stent was completely white. One year later, the color of the plaque at the site of the SES had changed to yellow. VLST, originating from the SES segment, occurred 9 years later. Angioscopic observations showed a dense yellow plaque, with red thrombi, at the site of the culprit lesion. In this case, the cause of VLST was considered to be the rupture of a neoatherosclerosis lesion. Thus, yellow neointima formation, after SES implantation, may be a risk factor for VLST. Indeed, Ueda et al. reported that yellow neointima formation, 1 year after DES implantation, resulted in worse prognoses than did the development of white neointima.14 Today, neoatherosclerosis is widely known to occur, even after BMS implantation. Another mechanism that is believed to induce LST and VLST is peri-stent contrast staining (PSS). PSS was firstly reported by Imai et al., and was reported to have a frequency, after 1st-G DES implantation, of approximately 1.9%; the VLST rate was significantly higher in patients with PSS than in those without PSS.15 Several mechanisms of VLST were considered to be associated with PSS, including outward remodeling due to DES-induced hypersensitivity reactions, diminished numbers of thrombi at the stent site, and mechanical stimulation resulting from fractured stent struts. We observed a typical case of PSS at an SES implantation site; angioscopy clearly demonstrated the thrombogenic potential that existed at the PSS site. Dense yellow plaque, with red thrombi, is clearly visible at the PSS site. In this case, the cause of the PSS was thought to be SES–induced inflammation. As described above, angioscopy played an important role in understanding plaque healing after 1st-G DES implantation. Figure 4 shows the mechanism of ISR and VLST development, based on our observations of angioscopy.

Second-generation (2nd-G) DESs

Considering the disadvantages of the 1st-G DESs, drug pharmacokinetics and drug-carrying polymers were improved for the next generation of DESs. In the fast-release zotarolimus-eluting stent (E-ZES), at least 90% of the drug releases within 2 weeks of stent implantation. Thus, drug release from E-ZESs occurs earlier than for 1st-G DESs. Therefore, the post-E-ZES implantation healing response occurs earlier than after 1st-G DES implantation, and mimics that of BMSs. Following E-ZES implantation, a thicker neointima covers the stent struts than that associated with 1st-G DESs.16 E-ZESs may also provide sufficient plaque sealing, similar to that associated with BMSs. The approaches used with everolimus-eluting stents (EESs) and slow

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**Fig. 3** A case of very late stent thrombosis. A 43-year-old man with stable angina pectoris received an elective sirolimus-eluting stent (SES) in his left circumflex artery. (A) Left coronary angiogram (spider view) (a–c) Angioscopic images immediately after percutaneous coronary intervention (PCI). The plaque color under the stent is completely white. (a–c’) Angioscopic images one year after PCI. The neointima color at the SES implant site is yellow with red thrombus (c’). (a–c’) Angioscopic images at the site of the very late stent thrombosis. Angioscopy reveals dense, yellow plaque, with massive red thrombi.16
release zotarolimus-eluting stents (R-ZESs) are different than those used with 1st-G DESs; the DESs also contain more bio-compatible polymer. Dai et al. reported that neointima coverage and thrombi formation, after 2nd-G DES implantations, are better than those following 1st-G DES implantations. Thus, the problems caused by the 1st-G DES stent polymers have largely been solved; however, some may remain. We often experienced the presence of thrombi in segments of EESs 1 year after their implantation in patients with ACS; residual thrombi continued to exist at the stented site. On the other hand, there were no thrombi in non-ACS lesions. In general, EESs are thought to provide better healing than 1st-G DESs; however, we caution against their use in ACS lesions.19)

Third-generation (3rd-G) DESs
Further development of the polymer technology resulted in the 3rd-G DESs that have an abluminal, bioabsorbable polymer that contains drug; the stent eventually becomes a BMS as the polymer is bioabsorbed. The drug is released within about 3 months and the polymer is fully absorbed 4–6 months after stenting. These devices seem to have better vascular healing and prevent early neointima formation. We are currently investigating the vascular response after 3rd-G DES implantation and comparing that with the responses following 2nd-G DES implantation. Our impression is that the neointima thickness, following 3rd-G DES implantation, is thicker than that which forms after 2nd-G DES implantation. However, the grade of yellow neointima is less than that associated with 2nd-G DESs. The answer to the question of which generation of DES is better remains unknown, currently.

In the near future, biodegradable vascular scaffolding will be available. Angioscopic observation of the healing process associated with these types of devices will be important to fully assess the safety of this new technology.

ISR after DES implantation
Since the introduction of DESs, the problem of ISR was thought to be almost completely solved; however, ISR is rarely experienced after DES implantation. The mechanism of early stage ISR, after BMS implantation, was thought to consist mostly of smooth muscle proliferation; white plaque is angioscopically visible at the ISR lesion. However, various mechanisms exist for the development of ISR, after DES implantation. One of these mechanisms is neoatherosclerosis. Figure 5 shows an ISR lesion, following SES implantation, in the mid-portion of a right coronary artery. Angioscopy revealed that the neointimal tissue was yellow, indicative of a so-called neoatherosclerosis. Integrated-backscatter intravascular ultrasound (IVUS) clearly indicated the presence of lipid-rich tissue in the ISR lesion. Effective treatments for DES–associated ISRs are uncertain, but include plain old balloon angioplasty, scoring balloon use, DES within a DES, BMS within a DES, and drug-coated balloon use.
We experienced that ISR lesion was treated using a BMS, with the expectation that the BMS would result in the sealing of the atheroma. In this case, the attempt was successful. Thick, white neointima covered the ISR lesion, without restenosis being observed at the follow-up examination. This case suggests that angioscopic observation directly impacts the choice of an effective therapy.

OCT and Angioscopy

Recent intravascular imaging procedures have frequently involved the use of OCT. Neointimal healing, after DES implantation, can be quantitatively assessed using OCT, and many investigators have reported and believed their OCT findings. Indeed, OCT can detect thin neointima-covered stent struts early after DES implantation; the thickness of the neointimal coverage can also be measured. However, the coverage of stent struts by layers of thrombi cannot be assessed using OCT, whereas angioscopy can clearly detect these thrombi. Figure 6 shows covered struts, 3 weeks after EES implantation. The struts were covered by a low-signal material, based on OCT determinations; therefore, we thought that the stent strut coverage was adequate after 3 weeks. We then performed angioscopy to observe the early-stage neointima. Unbelievably, the stent struts were covered by thin, red thrombi. This observation indicated that qualitative analyses using angioscopy, after stent implantation, are superior to those using other modalities.

Lotus-root Appearance Imaging by OCT

The angiographic appearance of haziness sometimes manifests as a lotus-root appearance when using and OCT. The mechanism responsible for this manifestation remains unclear, but it is thought to represent channel recanalization, after thrombosis. Angioscopy clearly shows that the cause of this lotus-root appearance is the presence of a fibrin net. Figure 7 shows angiographic haziness with moderate stenosis at the left anterior descending artery. To assess the lumen profile and plaque characteristics, we attempted an OCT evaluation that revealed a lotus-root appearance. To clarify this observation, we performed angioscopy, which clearly showed a fibrin net formation at the site. This fibrin net was thought to be a recanalized thrombus. Based on this observation, a scoring balloon was used to cut the fibrin net before stenting.

Tissue Protrusion Immediately after Stent Implantation

We sometimes experience tissue protrusions after stent implantations, especially in patients with ACS. IVUS and OCT clearly show the amount of tissue, probably thrombi and plaque, protruding between the struts; however, the precise characteristics of these tissue protrusions are unclear. Angioscopy clearly shows the tissue characteristics and suggests the necessity of post-intervention medication. Figure 8 shows post-stenting an-
Fig. 6  A case of everolimus-eluting stent implantation in the left anterior descending artery, 3 weeks prior to this study. Angiography shows no in-stent restenosis at the stented site. Optical coherence tomography revealed a thin neointima covering all of the stent struts (A–D). Angioscopic observation detected that some parts of the neointima consisted of thin red thrombus (C').

Fig. 7  Lotus-root structures. (a) Coronary angiography shows stenosis with haziness in the proximal left anterior ascending coronary artery. (b and c) Pre-procedure optical coherence tomography cross-sectional images showing the lotus-root appearance (asterisks). (B’) A pre-procedure coronary angioscopic image corresponding to image (B), showing the fibrin net. White arrows indicate communications between the lumen and the channels.\(^5\)
giographic, OCT, and angioscopic visualizations in a patient who underwent ACS intervention. Angiography shows in-stent haziness after stenting, resulting in the use of long balloon inflation. To assess the stenting site, OCT showed some amount of tissue protrusion; however, discriminating between thrombus and residual plaque was difficult. An angioscopic evaluation demonstrated that the protruding tissue mainly consisted of dense yellow plaque and red thrombi. In this case, in addition to dual anti-platelet therapy, anti-coagulation therapy was continued for 1 week and aggressive lipid-lowering therapy was started immediately after PCI.24)

Angioscopic Imaging of the Aorta

Recently, angioscopic observations of the aorta have been a focus in this field. Early detection of aortic atherosclerosis that leads to acute aortic syndrome is an important theme for preventing sudden cardiovascular deaths. Various thrombi and plaques have been observed on the aortic surface using angioscopy. Komatsu et al. reported various stages of plaque, including ruptured plaques and thrombi that exist on angiographically normal aorta.25) At first, these images were disbelieved because other modalities could not detect these phenomena. Aono et al. also reported that the atherosclerosis grade on the aorta was related to the degree of coronary atherosclerosis.26) These observations may help to resolve the mechanism of acute aortic syndrome.

Conclusion

Since the introduction of angioscopy, we have observed many surprising things in living people; this from a tool used to observe blood flow in a living condition. Seeing is believing. We will continue to use this sophisticated modality to find the wonders of the intravascular world.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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