Chapter 16
Peri-stent Contrast Staining

Kazuoki Dai and Masaharu Ishihara

Abstract Lack of contact between stent struts and underlying vessel surface, described as stent malapposition, is observed more frequently after implantation of drug-eluting stent (DES) than that of bare-metal stent. Several studies have suggested the potential relationship between the stent malapposition and late stent thrombosis (LST). On the coronary angiography, stent malapposition is recognized as peri-stent staining (PSS) that is contrast staining outside of the stent contour. Intravascular imaging modalities, including intravascular ultrasound and optical coherence tomography, can detect less extensive stent malapposition by their high resolution and the ability to provide the cross-sectional images of the vessel. Coronary angioscopy, the intravascular imaging of a different dimension, permits the direct visualization of the intimal surface and provides an opportunity to understand pathogenesis and clinical implication of PSS. Pathological examination showed hypersensitivities mainly composed of inflammation at the site of stent malapposition. Coronary angioscopy shows yellow plaque and thrombus at PSS site, suggesting underlying inflammation and high thrombogenicity. These findings support the relation of PSS to LST. Careful medications, including dual antiplatelet therapy and intensive statin therapy, should be warranted for prevention of LST in patients with PSS.

Keywords Peri-stent contrast staining • Stent thrombosis • Inflammation

Drug-eluting stents (DES) have dramatically reduced the incidence of restenosis and target vessel revascularization as compared with bare-metal stents (BMS) [1, 2]. Although DES has been used prevalently in the world, concern about the increased risk of late stent thrombosis (LST) after DES implantation is raised [3, 4].

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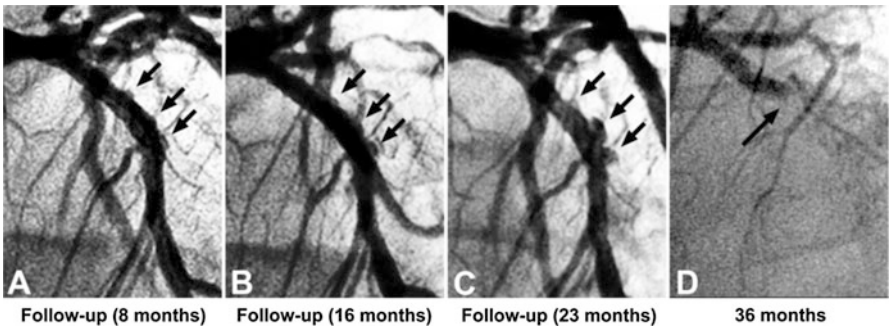
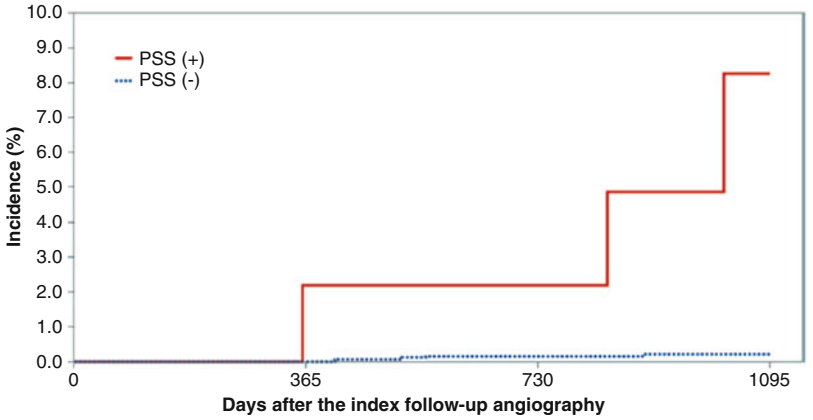


Fig. 16.1 Serial changes of contrast staining outside the sirolimus-eluting stent [7]. A 69-year-old man was treated with a SES (3.0 mm diameter × 33 mm long) implantation for chronic total occlusion lesion of LAD. (**a**) At 16 months after stenting, coronary angiography showed the areas of contrast staining outside the stent contour (PSS) (**b**) which increased in size at 23 months. (**c**) At 36 months after stenting, VLST of the SES occurred (**d**)

Lack of contact between stent struts and underlying vessel surface, so-called stent malapposition, is observed more frequently after implantation of DES than that of BMS. [5] Several studies have suggested the potential relation between stent malapposition and LST. [6] On the findings of coronary angiography, stent malapposition is recognized as peri-stent staining (PSS) that is contrast staining outside of the stent contour. Kon et al. reported that LST occurred several years after a sirolimus-eluting stent (SES) implantation in a patient with contrast staining outside a SES at follow-up coronary angiography (Fig. 16.1) [7]. Hypersensitivity reaction and chronic inflammation were found in the stent segment according to a pathological examination [7]. Previous study demonstrated that PSS was associated with late adverse events, such as restenosis or LST (Fig. 16.2) [8].

Intravascular imaging modalities, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), can detect less extensive stent malapposition due to their high resolution and the ability to provide the cross-sectional images of the vessel. On IVUS examination, PSS was recognized as stent malapposition, which was defined as separation of stent struts from the arterial wall with evidence of blood flow behind the strut except for a vessel bifurcation. Stent malapposition in late phase is formed by positive arterial remodeling, dissolution of residual thrombus or plaque debris, and chronic stent recoil [9, 10]. Previous IVUS studies showed that late acquired stent malapposition with positive remodeling was seen in 5–13 % of lesions treated with DES [11–13], and the stent malapposition was associated with the occurrence of LST. [6] On OCT examination, PSS was recognized as cavities between and outside the stent struts (Fig. 16.3). These cavities, uncovered struts, and red thrombus were frequently observed in the lesions with PSS compared with those without PSS. These findings suggested that PSS was associated with delayed healing and could be a risk factor for stent thrombosis.

Coronary angioscopy, the intravascular imaging of a different dimension, permits the direct visualization of the intimal surface and provides an opportunity to



Days	0	365	730	1095
PSS (+) N of lesions at risk	51	46	40	26
N of lesions with events	0	1	1	3
Cumulative incidence	0%	2.1%	2.1%	8.2%
PSS (-) N of lesions at risk	2761	2532	1847	580
N of lesions with events	0	0	3	4
Cumulative incidence	0%	0%	0.13%	0.2%

Fig. 16.2 Cumulative incidence of stent thrombosis after the index follow-up angiography: PSS group versus non-PSS group [8]. A 3-year cumulative incidence of subsequent definite stent thrombosis in the PSS group also was numerically higher than that in the non-PSS group (8.2 % vs. 0.2 %)

understand pathogenesis and clinical implication of PSS. We presented angioscopic images in two cases of PSS observed by coronary angiography. The first case is 77-year-old female with unstable angina pectoris who was treated with a paclitaxel-eluting stent (PES, 2.5 mm diameter × 20 mm long) at midportion of the left anterior descending artery 6 years ago. Follow-up coronary angiography showed no restenosis, but contrast staining outside the proximal site of stent segment, which is named PSS (Fig. 16.4). On coronary angioscopic examination, the struts at the proximal site of stent segment were exposed similar to immediately after implantation of the stent. Blood flow was observed behind stent struts. These findings showed that the struts were not covered by neointima and malapposed. Additionally, red thrombus on yellow plaque behind the malapposed struts was found. In the second case, 78-year-old female with stable angina pectoris was treated with SES (3.5 mm diameter × 18 mm long) implantation at midportion of right coronary artery 6 years ago. VLST unfortunately occurred during clinical follow-up in this case, and emergency coronary angiography at the time of VLST showed the occlusion of proximal site of the stent segment. After performing thrombus aspiration, coronary angiography showed TIMI-3 flow and appearance of PSS at proximal site of the stent segment (Fig. 16.5). Similar to the first case, coronary

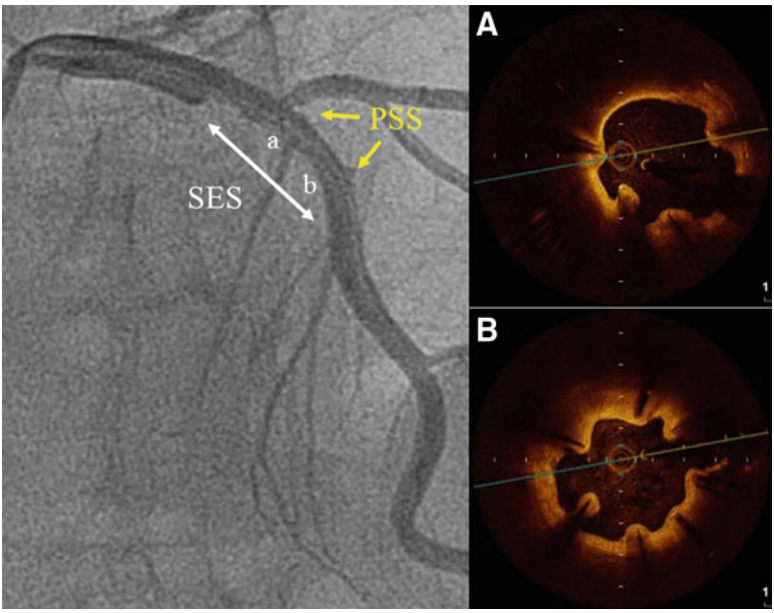


Fig. 16.3 Representative OCT findings at PSS sites. An 81-year-old male with acute myocardial infarction was treated with a SES (3.5 mm diameter × 18 mm long) at midportion of left anterior descending artery 10 years ago. Follow-up coronary angiography showed no restenosis, but contrast staining outside the proximal site of stent segment, which is named PSS. In OCT examination, many cavities between and outside the stent struts were observed

angioscopy showed that struts were uncovered and malapposed within the segment of PSS. There was red thrombus on yellow plaque behind the malapposed struts.

Ishihara et al. assessed angioscopic findings of 11 DES-implanted lesions of PSS on coronary angiography [14]. Neointimal coverage and existence of thrombus and/or yellow plaque were compared between PSS and non-PSS sites. Lower neointimal coverage and higher incidence of yellow plaque with thrombus were found at PSS sites compared with non-PSS sites. These findings suggested that delayed arterial healing and persisting inflammatory reaction resulted in thrombus formation at PSS sites. Also, they classified angiocsopic findings of PSS into 3 types. First, stent struts at PSS sites were not covered by neointima. Second, stent struts were covered by neointima, which could be seen only on the struts. Third, stent struts were covered by neointima, which was also observed between struts, but was partially absent. In the absence of neointimal coverage, blood flow between the stent and vessel wall was found and their space formed a cavity.

Pathological examination showed hypersensitivities mainly composed of inflammation at the site of late acquired stent malapposition [15, 16]. Coronary angioscopy shows yellow plaque and thrombus at PSS site, suggesting underlying inflammation and high thrombogenicity. These findings support the relationship between PSS and LST.

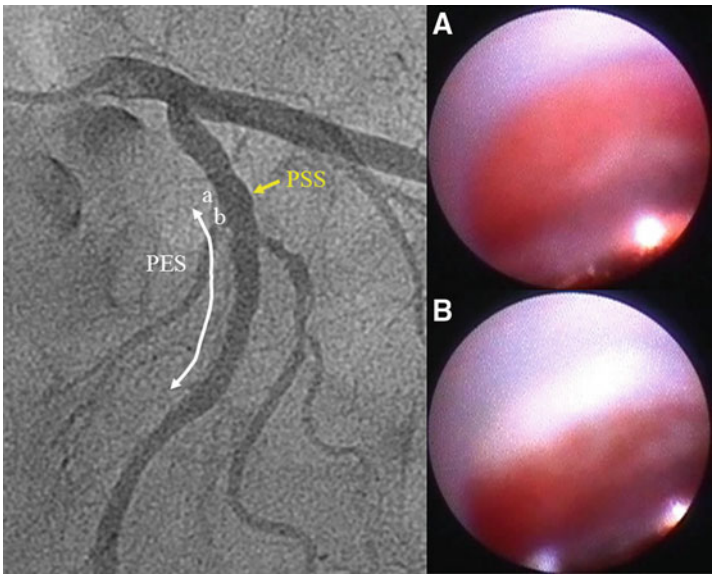


Fig. 16.4 Representative angioscopic findings at a PSS site in a patient underwent follow-up coronary angiography. The struts at the proximal site of stent segment were exposed similar to immediately after implantation. Blood flow was observed behind stent struts. These findings showed that struts were not covered by neointima and malapposed. On yellow plaque behind the malapposed struts, red thrombus was found

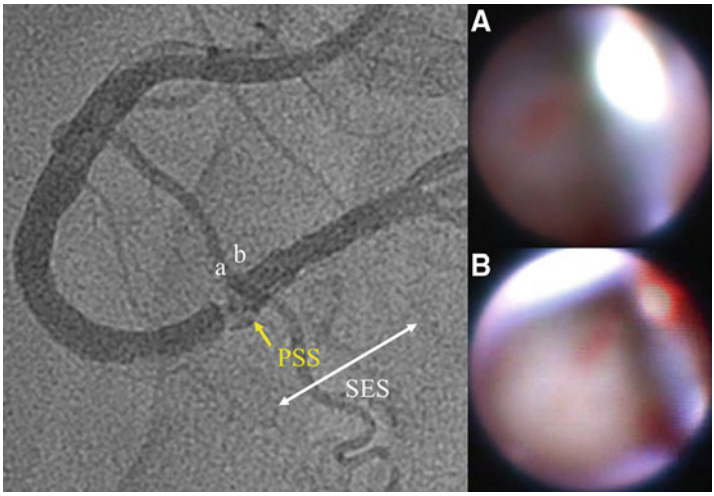


Fig. 16.5 Representative angioscopic finding at a PSS site in a patient with VLST. Emergency coronary angiography at the time of VLST showed the occlusion of proximal site of stent segment. After performing thrombus aspiration, coronary angiography showed TIMI-3 flow with contrast staining outside the proximal site of stent segment. Coronary angioscopy showed that struts were uncovered by neointima and malapposed. On yellow plaque behind the malapposed struts, red thrombus was found

PSS is not an infrequent phenomenon after the first generation of DES implantation, formed mainly by positive vessel remodeling caused by hypersensitivities and persisting inflammatory reaction. Angioscopically, PSS is associated with delayed neointimal coverage, higher grade of yellow plaque, and higher incidence of thrombus. These findings suggested that PSS may lead to the occurrence of VLST in the future. Careful medications, including dual antiplatelet therapy and intensive statin therapy, should be warranted for the prevention of LST in patients with PSS. Coronary angioscopy is a useful imaging device to assess the intimal surface after stenting and understand the pathogenesis of thrombus formation.

References

1. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Homes DR, O'Shaughnessy C, Caputo RP, Kereakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349:1315–23.
2. Morice MC, Serruys PW, Sousa JE, Fajadet J, Hayashi EB, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R, RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346:1773–80.
3. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, DOmburg RT, Hess OM, Boersma E, Meier B, Windecker S, et al. Early and late coronary thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007;369:667–78.
4. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004;364:1519–21.
5. Recalde SA, Moreno R, Barreales L, Rivero F, Galeote G, Valero JS, Calvo L, Lopez E, Sendon LJ. Risk of late-acquired incomplete stent apposition after drug-eluting stent versus bare-metal stent. A meta-analysis from 12 randomized trials. J Invasive Cardiol. 2008;20:417–22.
6. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation. 2007;115:2426–34.
7. Kon H, Sakai H, Otsubo M, Takano H, Okamoto K, Sato T, Kimura T, Inoue K. Contrast staining outside the sirolimus-eluting stent leading to coronary aneurysm formation: a case of very late stent thrombosis associated with hypersensitivity reaction. Circ Cardiovasc Interv. 2011;4:e1–3.
8. Imai M, Kadota K, Goto T, Fujii S, Yamamoto H, Fuku Y, Hosogi S, Hirono A, Tanaka H, Tada T, Morimoto T, Shiomi H, Kozuma K, Inoue K, Suzuki N, Kimura T, Mitsudo K. Incidence, risk factors, and clinical sequelae, of angiographic peri-stent contrast staining after sirolimus-eluting stent implantation. Circulation. 2011;123:2382–91.
9. Kozuma K, Costa MA, Sabate M, Serrano P, van der Giessen WJ, Ligthart JM, Coen VL, Levendag PC, Serruys PW. Late stent malapposition occurring after intracoronary beta-irradiation detected by IVUS. J Invasive Cardiol. 1999;11:651–5.
10. Mintz GS, Weissman NJ, Fitzgerald PJ. IVUS assessment of the mechanisms and results of brachytherapy. Circulation. 2001;104:1320–5.

11. Ako J, Morino Y, Honda Y, Hassan A, Sonoda S, Yock PG, Leon MB, Moses JW, Bonneau HN, Fitzgerald PJ. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. J Am Coll Cardiol. 2005;46:1002–5.
12. Hong MK, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. Circulation. 2006;113:414–19.
13. Siqueira DA, Abizaid AA, Costa Jde R, Feres F, Mattos LA, Staico R, Tanajura LF, Chaves A, Centemero M, Sousa AG, Sousa JE. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes. Eur Heart J. 2007;28:1304–9.
14. Ishihara T, Awata M, Fujita M, Watanabe T, Iida O, Ishida Y, Nanto S, Uematsu M. Angioscopic assessment of peri-stent contrast staining following drug-eluting stent implantation. Circ J. 2014;78:122–7.
15. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent; should we be cautious? Circulation. 2004;109:701–5.
16. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57:1314–22.