INTERNAL MEDICINE

Heterogeneous Intravascular Ultrasound Findings of Stent Thrombosis

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Abstract

Objective The underlying mechanisms of stent thrombosis are not completely understood.

Methods We experienced 12 definite stent thrombosis cases (1 early, 1 late, and 10 very late) at our hospital from July 2011 to April 2016 and evaluated the possible causes of stent thrombosis by intravascular ultrasound (IVUS).

Results Five different potential morphological causes of stent thrombosis (neoatherosclerosis, stent malapposition, stent fracture, edge dissection, and stent underexpansion) were detected by IVUS in 10 cases (83.3%); in 1 of the remaining 2 cases, the discontinuation of antithrombotic drugs resulted in early stent thrombosis without abnormal IVUS findings. Of the 12 stent thrombosis cases, 4 occurred at a bare-metal stent (average time from stent implantation, 106 months); in all 12, significant neointimal hyperplasia was observed on IVUS, and 2 had plaque ruptures at an in-stent or proximal reference. Malapposed stent struts were observed in three very-late stent thromboses, and all of these underwent sirolimus-eluting stent implantation. Stent thrombosis due to mechanical (stent fracture) or procedure-related complications (edge dissection and stent underexpansion) was observed in three cases.

Conclusion In patients with stent thrombosis, heterogeneous findings were observed in IVUS. This IVUS case series illustrates the possible mechanisms of stent thrombosis.

Key words: stent thrombosis, intravascular ultrasound, bare-metal stent, drug-eluting stent

Introduction

Stent implantation has been shown to reduce the rate of restenosis compared with balloon angioplasty alone; in particular, the use of drug-eluting stents has resulted in a dramatic reduction in the rate of neointimal formation over the last decade (1). However, concerns have been raised regarding stent thrombosis (2). Stent thrombosis is a rare but fatal complication of percutaneous coronary intervention (3-6). Therefore, the prevention of stent thrombosis is important in the clinical setting. Intravascular imaging and pathological studies have reported that various causes are associated with stent thrombosis, depending on stent types and time since implantation (7-9). Nevertheless, the underlying mechanisms of stent thrombosis are not completely understood. Accord-ingly, the aim of the present study was to investigate the possible causes of stent thrombosis using intravascular ultrasound (IVUS).

Materials and Methods

We retrospectively analyzed 601 consecutive patients who underwent percutaneous coronary intervention from July 2011 to April 2016 in Kitaishikai Hospital. The institutional review board approved the retrospective use of the patients' data. Definite stent thrombosis was diagnosed according to the Academic Research Consortium criteria (10). Early, late, and very-late stent thromboses were defined as follows: early stent thrombosis, 0-30 days; late stent thrombosis, 31 days-1 year; very-late stent thrombosis, >1 year post-stent implantation.

Table 1. Mechanisms of Bare-metal Stent Failure in 8 Lesions by Intravascular Ultrasound.

	Stent thrombosis (+)	(-)
Abnormal vascular response	**4**	**4**
-Neointimal hyperplasia	4	4
with plaque rupture	2	0
without plaque rupture	2	4
-Stent malapposition	0	0
Mechanical and procedure-related complications	**0**	**0**

Table 2. Mechanisms of Drug-eluting Stent Failure in 36 Lesions by Intravascular Ultrasound.

	Stent thrombosis (+)	(-)
Abnormal vascular response	**3**	**20**
-Neointimal hyperplasia	0	20
with plaque rupture	0	0
without plaque rupture	0	20
-Stent malapposition	3	0
Mechanical and procedure-related complications	**3**	**8**
-Stent underexpansion	1	8
-Others	2	0
Unkown cause	**2**	**0**

Intravascular ultrasound

IVUS imaging was performed after intracoronary administration of 0.1-0.2 mg nitroglycerin using a commercially available IVUS system (iLab with 40-MHz Atlantis SR Pro catheters, Boston Scientific, Fremont, CA, USA; or VISI-WAVE with 40-MHz Viewit catheters, Terumo, Tokyo, Japan) with automatic pullback at 0.5 or 1.0 mm/s. If necessary, at the operator's discretion, we used an aspiration catheter or small-sized balloon to open the occluded artery or severe stenosis before the IVUS examination. IVUS analyses were performed through the agreement of two independent cardiologists (TM and SI), who were blinded to the clinical data, stent type, and time of occurrence of the stent thrombosis. Regarding the definitions for the IVUS qualitative analysis, plaque rupture was defined as a cavity that communicated with the lumen with an overlying residual fibrous cap fragment (11); stent malapposition was defined as blood speckle behind the stent struts that did not overlie a side branch (12); and complete stent fracture was defined as complete separation of the stent into ≥2 pieces separated by image slices with no visible stent struts (13).

The statistical analysis was performed using the StatView 5.0 software program (SAS Institute, Cary, NC, USA). Continuous variables were displayed as median values with the interquartile range (IQR; first and third) and compared between groups using the Mann Whitney U test. Values of p< 0.05 were considered statistically significant.

Results

In the present study, stent failure which needed target lesion revascularization was seen in 45 lesions of 43 patients, which were treated with 36 drug-eluting stents (DESs), 8 bare-metal stents (BMSs), and 1 unknown stent. Of the lesions with stent failure, stent thrombosis occurred in 12 lesions (26.7% per lesion) of 12 patients (27.9% per patient). The mechanism of stent failure was able to be identified by IVUS in 43 lesions (95.6%). In the BMSs, the mechanism of stent failure was only due to an abnormal vascular response (neointimal hyperplasia). Regarding the abnormal vascular response, stent malapposition was not observed in any of the cases of BMS failure. Plaque rupture, which is the most common cause of coronary thrombosis, was detected only in the lesions with stent thrombosis (Table 1). In contrast, heterogeneous IVUS findings were seen in the cases of DES failure, especially in the lesions with stent thrombosis, where an abnormal vascular response was observed in 20 lesions by IVUS. All 20 of these stent failures were due to neointimal hyperplasia without plaque rupture, while stent malapposition was not detected. In contrast, in the lesions with stent thrombosis, the mechanism of stent failure by an abnormal vascular response was only stent malapposition (Table 2).

Stent failure due to mechanical and procedure-related complication occurred earlier than those instances of failure due to abnormal vascular response (449 [IQR, 252-739] vs. 2,396 [1,016-3,124] days, p=0.0011). Furthermore, stent failure in the DES-treated lesions occurred earlier than in the BMS-treated lesions (1,016 [IQR, 338-2,342] vs. 3,927 [3,185-4,590] days, p<0.0001). Even when the comparison was limited to the lesions with an abnormal vascular response, similar results were obtained (DES vs. BMS; 1,455 [IQR, 742-2,978] vs. 3,927 [3,185-4,590] days, p=0.0005).

The findings of the 12 patients with stent thrombosis are summarized in Table 3. In the present study, IVUS revealed various possible causes of stent thrombosis (neoatherosclerosis, stent malapposition, stent fracture, edge dissection, and

Table 3. Findings in 12 Patients with Stent Thrombosis.

Patient No.	Age/sex	Clinical presentation at index procedure	Clinical presentation at stent thrombosis	Culprit vessel	Antithrombotic drugs	Stent	Duration from stent implantation (months)	Possible cause of stent thrombosis using IVUS
Bare-metal stent								
No.1 (Fig. 1)	61/M	EAP	STEMI	RCA	Aspirin 100 mg	BMS	107	Neointimal plaque rupture
No.2 (Fig. 2)	67/M	STEMI	STEMI	LAD	Aspirin 200 mg	BMS	96.8	Proximal reference plaque rupture
No.3	78/M	EAP	NSTEMI	RCA	Aspirin 200 mg Clopidogrel 75 mg	BMS	125	Neointimal hyperplasia
No.4	64/M	STEMI	STEMI	RCA	Aspirin 81 mg	BMS	95.5	Neointimal hyperplasia
Drug-eluting stent								
No.5 (Fig. 3)	46/M	STEMI	STEMI	LAD	Aspirin 100 mg	SES	55.9	Malapposition due to positive remodeling
No.6	84/M	EAP	STEMI	LAD	Aspirin 100 mg	SES	101.4	Malapposition due to positive remodeling
No.7	68/F	unknown	STEMI	LAD	None	SES	55	Malapposition
Mechanical and procedure-related complications								
No.8 (Fig. 4)	89/M	STEMI	STEMI	LAD	Aspirin 81 mg	SES	67.6	Stent fracture
No.9 (Fig. 5)	85/F	NSTEMI	NSTEMI	LCX	Aspirin 100 mg Clopidogrel 75 mg	CoCr-EES	6.6	Stent edge dissection
No.10 (Fig. 6)	87/M	EAP	STEMI	LAD	Aspirin 100 mg Clopidogrel 50 mg	SES	47.5	Stent underexpansion
Unknown cause by IVUS								
No.11 (Fig. 7)	86/M	EAP	STEMI	LAD	None	PtCr-EES	0.6	None
No.12	75/F	EAP	STEMI	RCA	Aspirin 100 mg Clopidogrel 25 mg	PES	49.6	None

BMS: bare-metal stent, CoCr-EES: cobalt-chromium everolimus-eluting stent, EAP: effort angina pectoris, F: female, Fig: figure, IVUS: intravascular ultrasound, LAD: left anterior descending artery, LCX: left circumflex artery, M: male, NSTEMI: non-ST-segment elevation myocardial infarction, PES: paclitaxel-eluting stent, PtCr-EES: platinum-chromium everolimus-eluting stent, RCA: right coronary artery, SES: sirolimus-eluting stent, STEMI: ST-segment elevation myocardial infarction

stent underexpansion). Of the 12 definite stent thrombosis cases, we will present the 7 cases that illustrate the different causes of stent thrombosis.

Case Nos. 1 and 2: Neoatherosclerosis (neointimal and proximal reference plaque rupture)

Case No. 1 (Fig. 1): Neointimal plaque rupture

A 61-year-old man was implanted with two overlapping BMSs (3.5×23 and 3.5×13 mm) in the proximal right coronary artery for effort angina pectoris. After 107 months, the patient was admitted to our hospital because of sudden chest pain. Emergency coronary angiography showed total occlusion proximal to the BMS site. After thrombus aspiration, IVUS was performed, and neointimal plaque rupture was observed.

Case No. 2 (Fig. 2): Stent proximal reference plaque rupture

A 67-year-old man was implanted with three BMSs (3.0× 12, 3.0×15, and 3.5×16 mm) in the mid-left anterior descending coronary artery (LAD) for ST-segment elevation myocardial infarction. After 96.8 months, the patient was admitted to our hospital because of sustained chest discomfort. Emergency coronary angiography showed total occlusion within 5 mm of the site of the stent's proximal edge. After balloon angioplasty and thrombus aspiration, IVUS was performed, and stent proximal reference plaque rupture was observed.

### Case No. 5 (Fig. 3): Late-acquired stent malapposition

A 46-year-old man was implanted with a 3.0×23-mm sirolimus-eluting stent (SES) at the proximal portion of the LAD for ST-segment elevation myocardial infarction. After 55.9 months, the patient was admitted to our hospital because of sustained chest pain. Emergency coronary angiography revealed a total occlusion distal to the SES-implanted site. IVUS was performed after thrombus aspiration and balloon angioplasty. Stent malapposition was observed, while post-procedural IVUS images at the index intervention showed well-apposed stents.

Case No. 8 (Fig. 4): Complete stent fracture

An 89-year-old man was initially implanted with a 3.0× 28-mm SES in the mid-LAD for ST-segment elevation myocardial infarction. A second procedure was performed six months after the index SES placement because of lesion progression at the stent proximal site. In the second procedure, the patient was implanted with a 3.0×18-mm SES, which overlapped the old stent. At 67.6 months after the first procedure, the patient was admitted to our hospital because of sustained chest pain. Emergency coronary angiography revealed obvious stent fracture at the site of total occlusion near the overlapping site. IVUS was performed after thrombus aspiration and balloon angioplasty, confirming complete separate stent fracture with displacement.

Case No. 9 (Fig. 5): Progression of stent edge dissection

An 85-year-old woman was implanted with a 2.25×23-
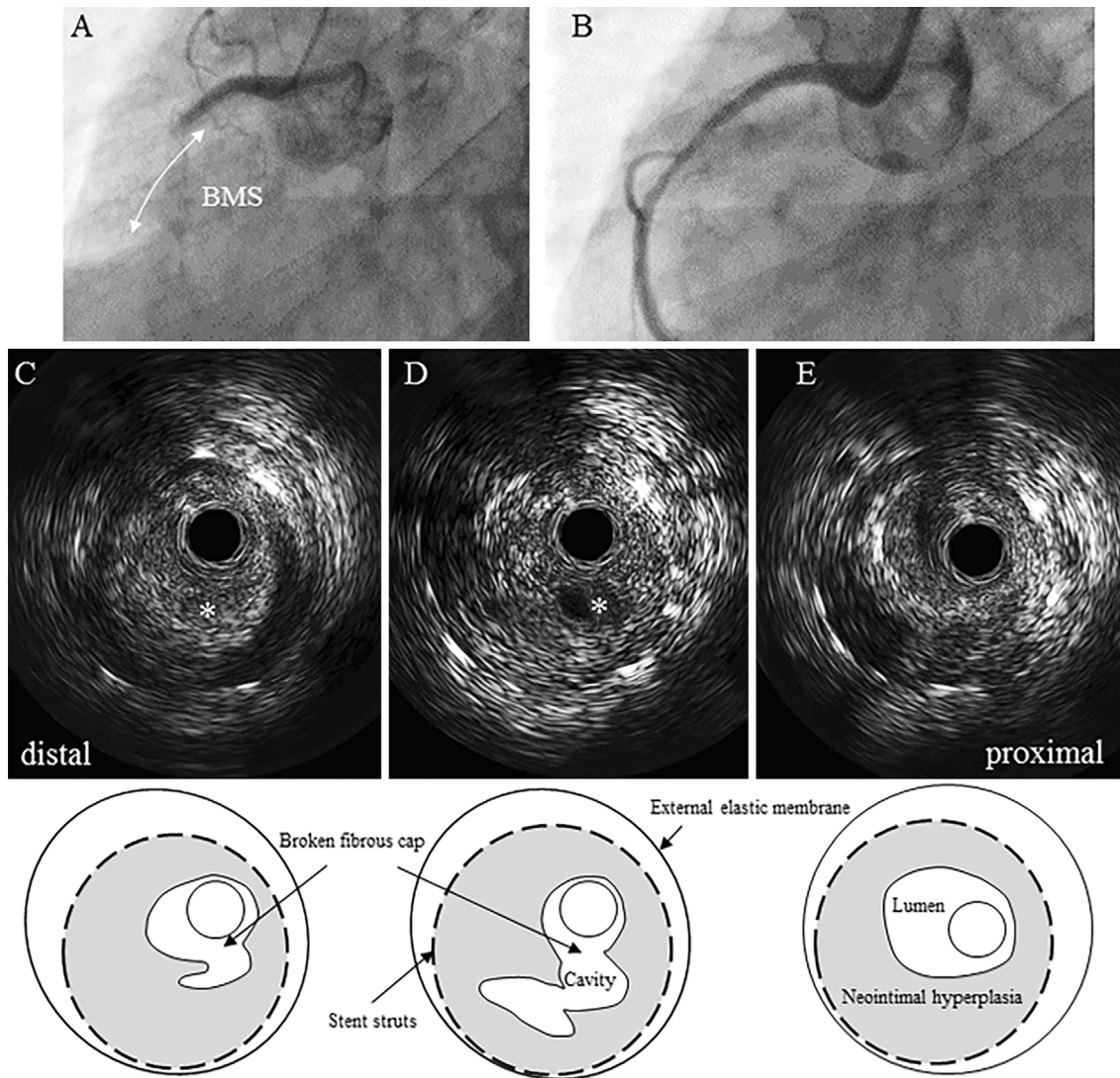
Figure 1. **A: Coronary angiogram of the right coronary artery showing total occlusion at the proximal part of the bare-metal stent. B: Coronary angiogram after thrombus aspiration. C-E: Intravascular ultrasound images showing in-stent neointimal hyperplasia (C-E) with a ruptured cavity (D, asterisk).**

mm cobalt-chromium everolimus-eluting stent (CoCr-EES) in the proximal left circumflex artery for non-ST-segment elevation myocardial infarction. After 6.6 months, the patient was admitted to our hospital because of resting angina with troponin elevation. Coronary angiography showed subtotal occlusion with thrombosis in myocardial infarction (TIMI) grade 2 flow from the stent proximal reference site. IVUS revealed edge dissection that was already observed at the index intervention. Proximal edge dissection at the index intervention reached the media, although there were no flow-limiting obstructions or significant abnormalities shown by angiography (TIMI 3 flow).

Case No. 10 (Fig. 6): Chronic stent underexpansion

An 87-year-old man was implanted with a 2.5×13-mm SES in the proximal LAD for effort angina pectoris. After 47.5 months, the patient was admitted to our hospital because of sudden chest pain. Emergency coronary angiogra-

phy revealed total occlusion at the SES-implanted site. After thrombus aspiration, IVUS was performed and revealed stent underexpansion (minimum stent area [MSA] =3.8 mm^2). We confirmed that MSA at the index procedure was 4.0 mm^2, indicating chronic stent underexpansion, not stent recoil.

Case No. 11 (Fig. 7): Discontinuation of antithrombotic drugs

An 86-year-old man was successfully implanted with a 3.0×16-mm platinum-chromium (PtCr) EES for effort angina pectoris. After discharge, the patient stopped taking antithrombotic drugs (clopidogrel and aspirin). Seven days after interruption of antiplatelet therapy (18 days after stenting), the patient was admitted to our hospital because of cardiogenic shock. Emergency coronary angiography showed thrombogenic occlusion at the stent site. IVUS was performed after thrombus aspiration and revealed thrombus-like appearances with no possible causes of stent thrombosis.
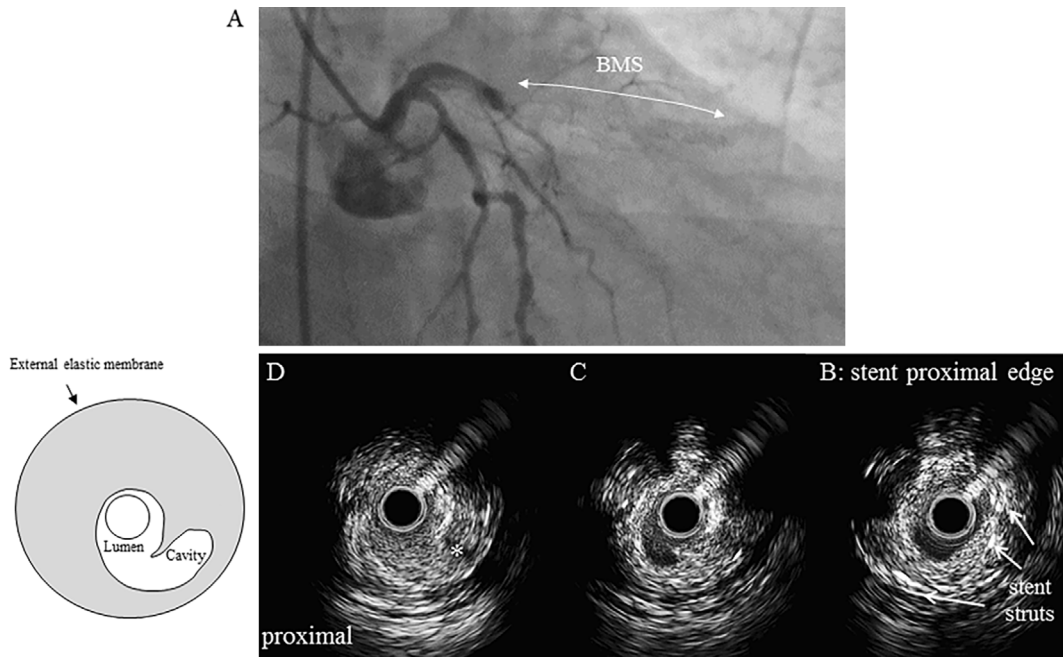
Figure 2. **A: Coronary angiogram of the left anterior descending coronary artery showing total occlusion. B-D: Intravascular ultrasound images showing plaque rupture (asterisk) at the site of proximal reference adjacent to significant neointimal hyperplasia.**
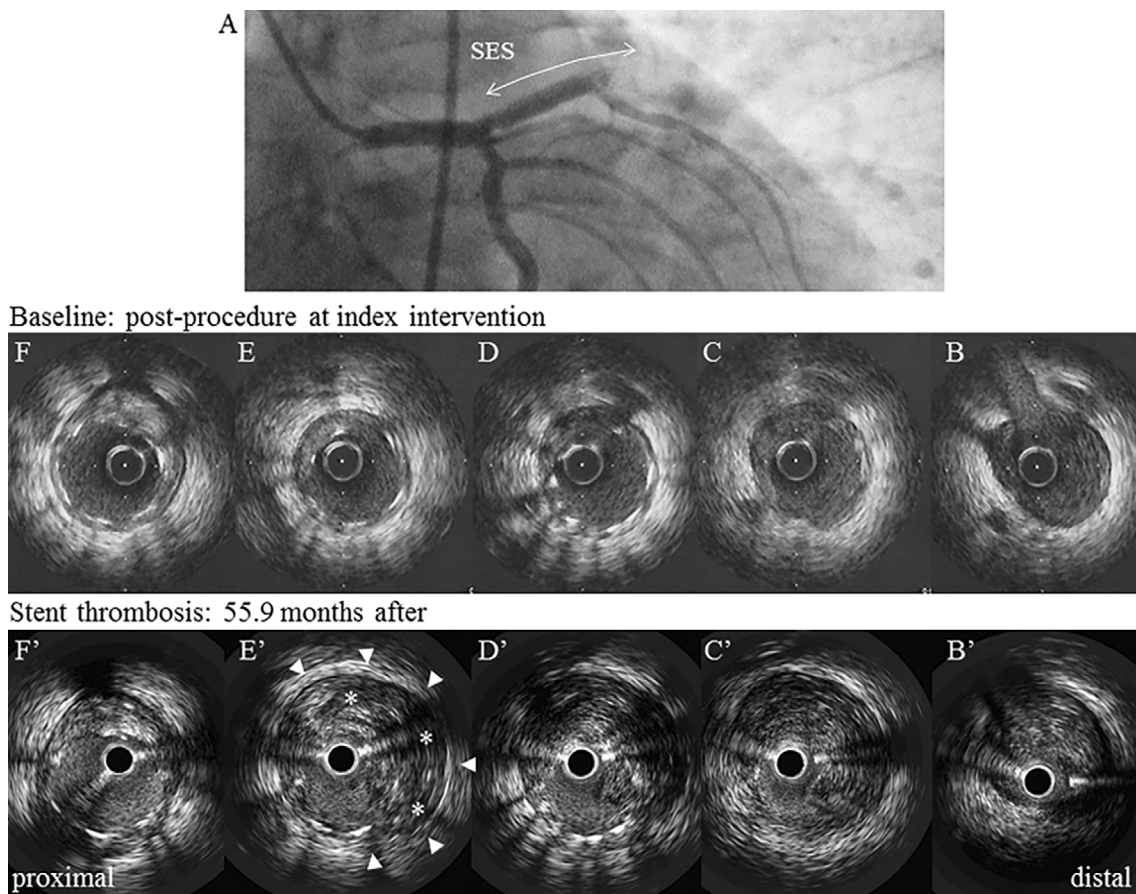
Figure 3. **A: Coronary angiogram of the left anterior descending coronary artery showing total occlusion. B-F: Post-procedure intravascular ultrasound (IVUS) images at the index intervention showing no stent malapposition. B'-F': IVUS images at the stent thrombosis corresponding to the baseline IVUS images (B-F) showing stent malapposition (asterisk). The same location of the external elastic membrane cross-sectional area (E and E') was markedly enlarged, from 11.4 to 25.8 mm², suggesting development of late-acquired stent malapposition due to positive remodeling (white arrowheads).**
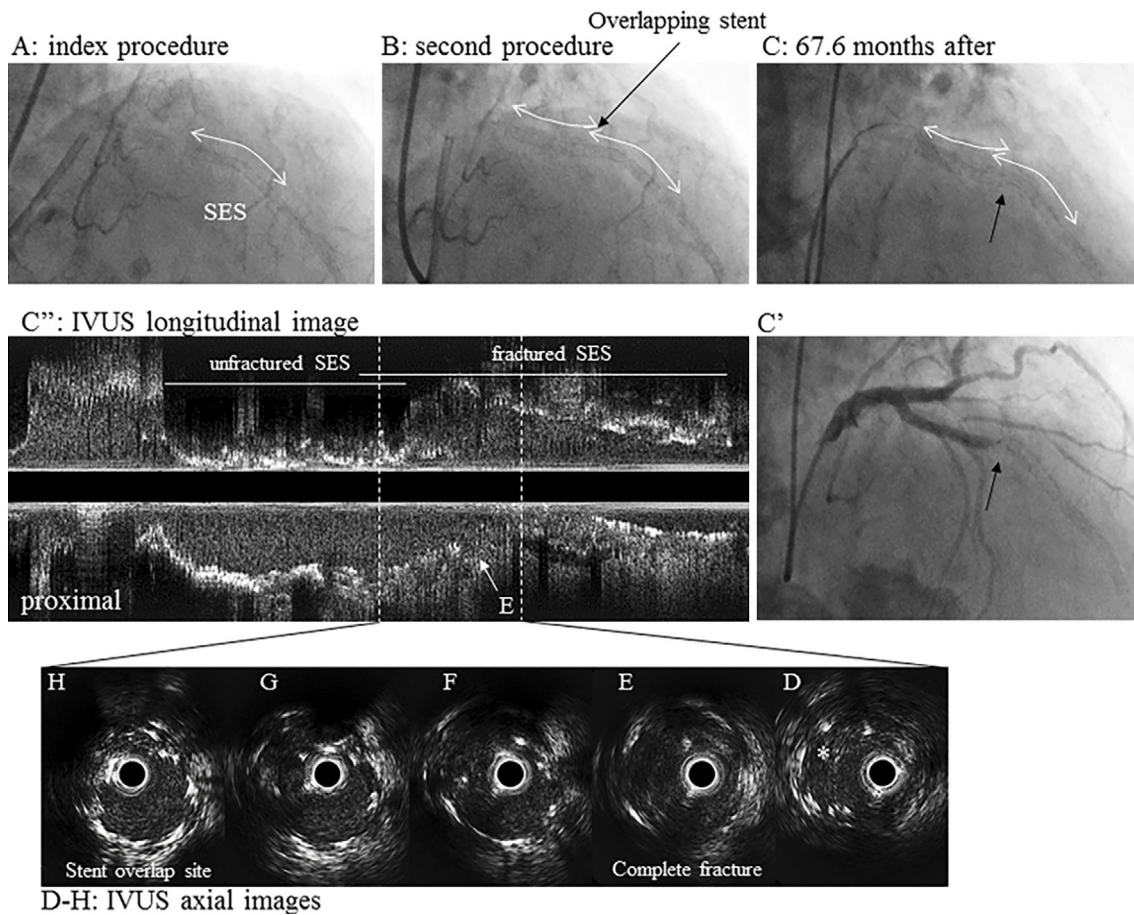
Figure 4. **A: Coronary angiogram of the left anterior descending coronary artery without dye at the index procedure. B: Coronary angiogram without dye at the second procedure. C-C': Coronary angiogram without (C) and with dye (C') at 67.6 months after the first procedure showing stent fracture (black arrow). C": Intravascular ultrasound (IVUS) longitudinal image confirming stent fracture (white arrow). D-H: IVUS axial images at fracture site corresponding to C". (E) Complete separation of the single stent indicating complete stent fracture, (H) double layered stent struts indicating stent overlap. *thrombus-like appearance.**

Discussion

The main findings of the present study are as follows: (1) Of the lesions with stent failure, the frequency of stent thrombosis was 26.7%, and stent thrombosis in 21.9% was due to abnormal vascular response and in 27.3% due to mechanical and procedure-related complications; (2) the timing of stent failure might depend on its mechanisms and stent types; and (3) heterogeneous IVUS findings were more commonly observed in the patients with DES failure with stent thrombosis than in those with BMS failure with stent thrombosis. Although only neointimal hyperplasia was found to be a mechanism of BMS failure, half of the lesions with stent thrombosis had plaque rupture, which can trigger thrombosis.

Abnormal vascular response

Pathological studies have revealed that the major cause of very-late stent thrombosis is an abnormal vascular response

(i.e. hypersensitivity reaction, excessive fibrin deposition, and neoatherosclerosis) (8, 9). We experienced seven cases (Nos. 1-7) in which an abnormal vascular response (neoatherosclerosis and malapposition) may have been associated with the development of very-late stent thrombosis.

Neoatherosclerosis

This concept was proposed by Nakazawa et al. based on pathological observations (8). Their group named newly formed atherosclerotic changes within the neointimal tissue of stented segments "neoatherosclerosis." Although neoatherosclerosis can develop after both BMS and DES implantation, it has been reported more frequently and earlier with DESs than in BMSs. However, unstable lesions characterized as thin-cap fibroatheroma or plaque rupture are more common with BMSs than DESs (8, 9); this was confirmed by IVUS and optical coherence tomographic studies (14, 15) and may be due to the longer time from stent implantation with BMSs than DESs. In the present study, two neointimal plaque ruptures with BMSs were detected using IVUS, and
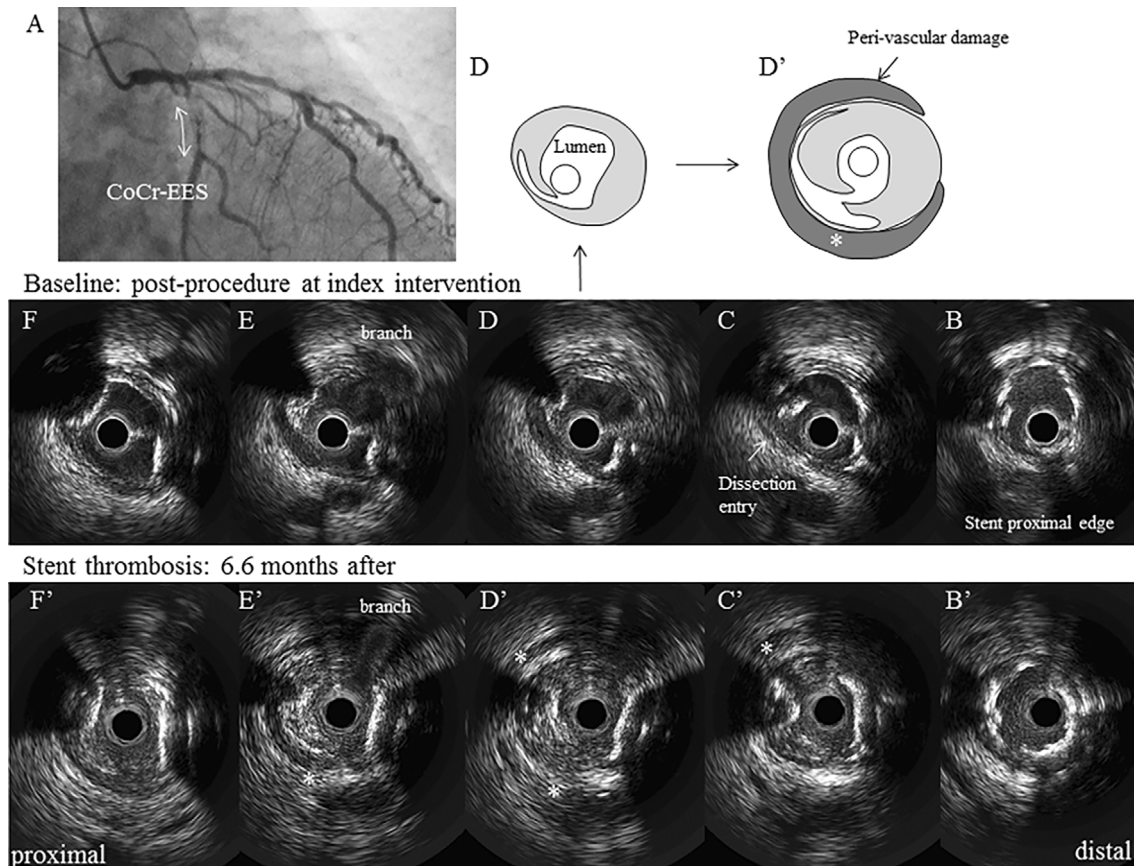
Figure 5. A: Coronary angiogram of the left circumflex artery showing subtotal occlusion. B-F: Post-procedural intravascular ultrasound (IVUS) images at the index intervention showing proximal edge dissection that reached the media. B'-F': IVUS images at the stent thrombosis corresponding to baseline IVUS images B-F showing unhealed dissection with perivascular damage (asterisk). Dissection was observed in panel F' at the stent thrombosis and was not present in the corresponding IVUS image (panel F at baseline), indicating longitudinal progression of edge dissection after the index procedure.

more than eight years had passed since the BMSs were initially implanted.

Stent malapposition

Late-acquired stent malapposition was far more commonly observed with DESs, particularly in SESs, than BMSs; this may have been associated with very late stent thrombosis (12, 15-17). All of our cases of stent malapposition (Nos. 5-7) had received SES implantation and were described as very-late stent thrombosis (average time from stent implantation =71 months). In two of the three cases involving stent malapposition, we confirmed late-acquired stent malapposition due to positive vessel remodeling compared with the findings at the index IVUS procedure. Indeed, IVUS studies have revealed the main mechanism of late-acquired stent malapposition to be positive vessel remodeling (12, 18, 19). Our present findings were consistent with those of previous reports. Furthermore, pathological studies have suggested that inflammation due to a hypersensitive reaction is a mechanism of positive vessel remodeling (20-22). These reports and the findings from the present cases suggest that there should be careful long-term follow-up of lesions with late-acquired stent apposition, particularly in cases of SES use.

Stent mechanical complication: Stent fracture

The reported frequency of stent fracture in previous studies using angiographic and/or IVUS analysis is 0.8-7.7% (23) and is much higher, up to 29%, by autopsy study (24). An IVUS study revealed that stent fracture was commonly observed in patients with stent thrombosis (16). Furthermore, a pathological study demonstrated an association between thrombosis and stent fracture (24), which is also supported by case reports (25, 26). It has been reported that the use of SESs is an independent risk factor for stent fracture, while stent fracture can occur in both BMSs and DESs (24). An IVUS study noted that complete separation is a frequent finding in SES fracture (13). In addition to SES use, longer stent length and overlapping stents are also recognized as contributors to stent fracture (24). Our case (No. 8) well illustrates these characteristics of SES fracture leading to stent thrombosis.
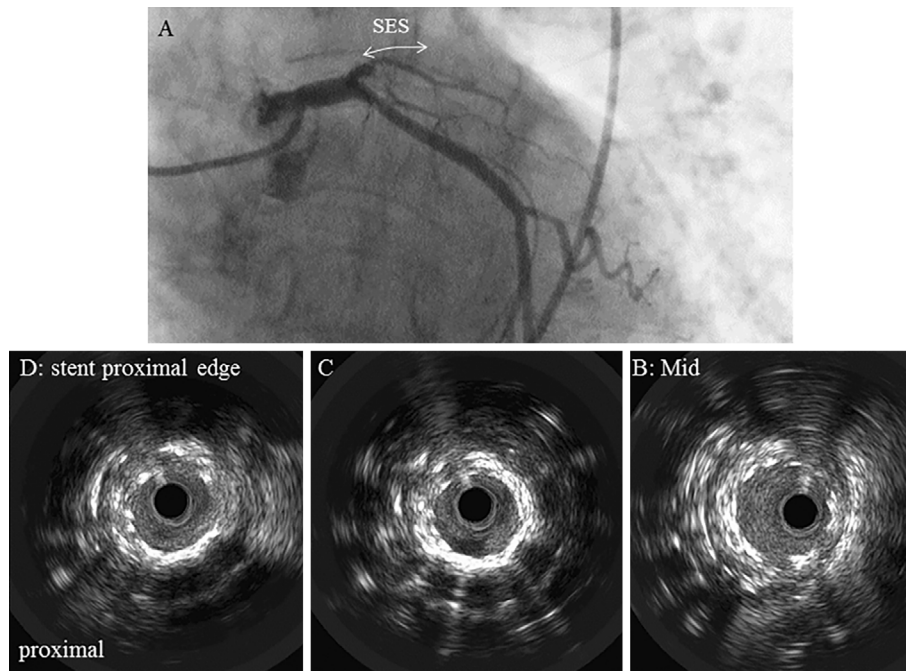
Figure 6. **A: Coronary angiogram of the left anterior descending coronary artery showing total occlusion. B-D: Intravascular ultrasound images showing stent underexpansion (the minimum stent area in panel C was 3.8 mm^2) without significant neointimal hyperplasia.**

Procedure-related complications

Persistent dissections and slow flow, thrombus, stent underexpansion, tissue prolapse, and residual stenosis have been suggested as procedure-related contributing factors to stent thrombosis (27-30). Of these factors, we experienced persistent dissection and stent underexpansion.

Edge dissection

Although coronary dissection after percutaneous coronary intervention is not a rare complication, its detection and precise evaluation have an impact in a clinical setting, as it has been reported that coronary dissections are associated with adverse cardiovascular events (30, 31). A pathological study suggested that exposure of connective tissue to blood speckle in the lumen due to dissection may result in the progression of thrombus formation (32). Coronary dissections can cause perivascular trauma, including hematoma, and subsequently flow-limiting obstruction (33-35). Furthermore, previous IVUS studies have demonstrated an association between edge dissection and early stent thrombosis (27, 30). In our case (No.9), persistent dissection that reached the media at the proximal stent edge was observed in postprocedure IVUS of index percutaneous coronary intervention. IVUS at the stent thrombosis revealed longitudinal progression of the dissection and perivascular damage, suggesting communication between the lumen and the perivascular space. Previous reports may help clarify why stent thrombosis developed in this case. Interestingly, in this case, stent thrombosis occurred at 6.6 months after stent implantation, indicating "late" stent thrombosis. The findings from the present case suggested that longitudinal progression of the dissection might be the cause of late stent thrombosis.

Chronic stent underexpansion

Studies have demonstrated that stent underexpansion commonly contributes to BMS restenosis and that the main mechanisms of restenosis were chronic stent underexpansion and neointimal hyperplasia in the DES era (36, 37). In addition, Fujii et al. demonstrated that stent underexpansion was one of the independent predictors of stent thrombosis (38). Thus, it was recognized that stent underexpansion contributed to stent failure, restenosis, and stent thrombosis. However, Liu et al. suggested that underexpansion related to stent thrombosis was more severe and occurred at a more proximal location than that related to restenosis (39). The findings from our case (No. 10) were consistent with the previous report. In this case, by comparing the IVUS findings at the index procedure and at stent thrombosis, we confirmed chronic stent underexpansion without significant proliferation of neointimal hyperplasia. We therefore concluded from IVUS that the probable cause of stent thrombosis in this case was chronic severe stent underexpansion.

Limitations

The present study had several limitations. A major limitation was that it involved a retrospective analysis, so the frequency of stent thrombosis could not be determined, and the number of stent thrombosis cases was small. Because of its resolution, grayscale IVUS is limited in characterizing neointimal hyperplasia compared with optical coherence tomography. In one of three cases with stent malapposition,
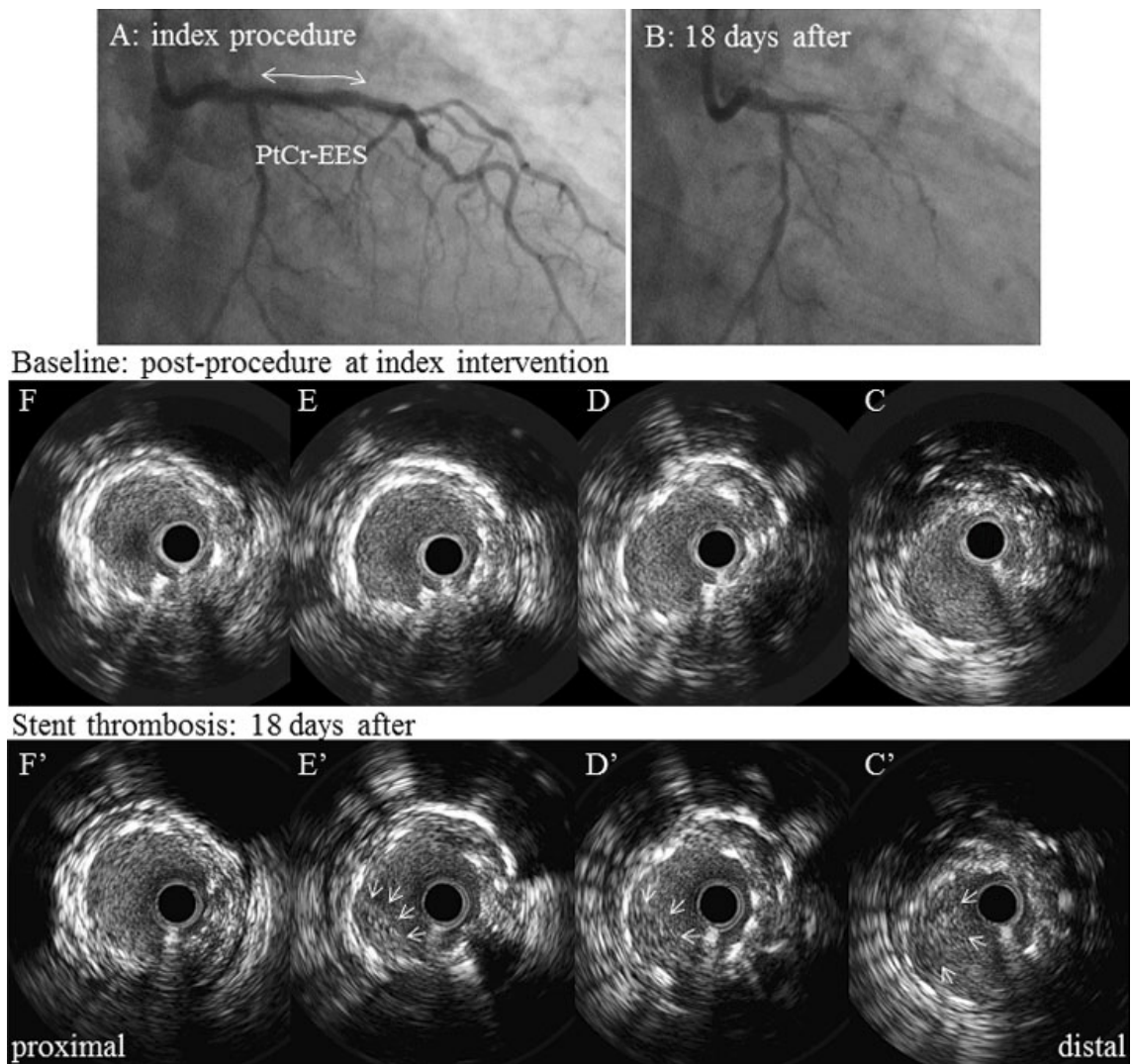
Figure 7. **A: Coronary angiogram of the left anterior descending coronary artery at the index procedure. B: Coronary angiogram 18 days after the index procedure showing total occlusion. C'-F': Intravascular ultrasound (IVUS) images at the stent thrombosis showing thrombus-like appearances (white arrows); no other cause of stent failure was revealed by IVUS, compared with baseline IVUS images (C-F, corresponding to follow-up C'-F').**

baseline procedural IVUS was not conducted; therefore, we were unable to conclude the cause of stent thrombosis: acute stent malapposition during the index procedure or late-acquired stent malapposition.

Conclusion

We experienced 12 definite stent thrombosis cases and evaluated the possible causes of stent thrombosis from IVUS observations. In patients with stent thrombosis, heterogeneous findings were observed in IVUS, especially in DES-treated lesions. Complex plaque morphology (rupture and malapposition) might have contributed to the occurrence of stent thrombosis. IVUS imaging insights from this case series regarding the development of stent thrombosis provide reliable information for understanding the underlying mechanisms and may help to determine a treatment strategy.

The authors state that they have no Conflict of Interest (COI).

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