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Original article

Serial intravascular ultrasound assessment of very late stent thrombosis after sirolimus-eluting stent placement

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ABSTRACT

Purpose: In-stent restenosis has been decreasing through the introduction of drug-eluting stents (DES). On the other hand, adverse events such as very late stent thrombosis (VLST) and late catch-up phenomenon can occur especially with sirolimus-eluting stents (SES, first-generation DES) in long-term follow-up. However, the precise mechanisms underlying VLST have not been well investigated *in vivo*.
Methods and results: From 2004 to 2010, 2034 SES were implanted in 1656 patients and caused eight VLST (0.48% per patient) at Fukuoka Tokushukai Medical Center. Of these, serial intravascular ultrasound (IVUS) images (post-stent implantation and at the time of VLST onset) were obtained from three patients with VLST. Comparing them with eight control patients with SES implanted, the vascular reactivity of VLST patients was analyzed. Eight VLST happened 50 ± 15 months after stent implantation and three of the eight patients with VLST had not taken aspirin daily. There were no differences in minimum stent area, maximum external elastic membrane (EEM) area, and stent edge (distal and proximal) EEM area in post-procedural IVUS images. Compared with the control group patients, ΔEEM area ($10.6 \pm 3.4\,mm^2$ vs. $1.7 \pm 1.9\,mm^2$, $p = 0.01$) and vessel expansion ratio ($185.6 \pm 40.3\%$ vs. $112.0 \pm 12.1\%$, $p = 0.01$) were significantly greater in the VLST group based on the greater peri-stent plaque expansion ($262.1 \pm 72.8\%$ vs. $118.7 \pm 21.2\%$, $p = 0.01$).
Conclusion: Our serial IVUS study showed that the vascular positive remodeling after SES implantation is one of the most probable morphological mechanisms for VLST development.

In-stent restenosis has decreased with the use of drug-eluting stents (DES). However, it became clear that some problems had occurred with first-generation DES in long-term follow-up such as very late stent thrombosis (VLST) and late catch-up phenomenon [1]. VLST is one of the most devastating events of DES, and VLST more often occurred especially with sirolimus-eluting stents (SES; Cypher™ or Cypher Select™ or Cypher Select Plus™, Cordis, Johnson & Johnson, Warren, NJ, USA). In Japan, VLST after SES implantation occurred at a rate of 0.26%/y without attenuation up to 5-year follow-up [2]. Different from other DES, previous studies demonstrated that SES-implanted coronary arteries had more positive remodeling because of inflammation by stent polymer and drug and that SES had often been malapposed [3,4]. However, there were few reports that delineated precise vessel response after SES implantation using serial intravascular imaging tools performed both at stent implantation and at the onset of VLST.

Intravascular ultrasound (IVUS) provides real-time, *in vivo*, cross-sectional imaging of whole coronary arterial wall structure before and after stent implantation and at follow-up [5,6].

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Especially in Japan, IVUS-guided coronary intervention has been widely distributed in real-world clinical practice, even during emergency procedures such as primary intervention for VLST. Therefore, the aim of the present study was to use IVUS images to elucidate vessel response of SES-implanted segments as one of the morphological mechanisms underlying post-SES VLST.

Methods

Study population and patient demographic data

From August 2004 to January 2010, 2034 SES were implanted in 1656 patients and eight VLST occurred at Fukuoka Tokushukai Medical Center (0.48% per patient, Table 1). In all the eight patients, VLST developed as an acute coronary syndrome and was diagnosed as VLST by angiography. Based on the Academic Research Consortium (ARC) definition, all VLST patients were thus classified as having definite stent thrombosis: 'symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis, occurring over 12 months after stent implantation [7].' Serial IVUS images (post-stent implantation and at the time of VLST onset) were obtained from three of these eight VLST patients. The remaining five VLST patients were excluded from this study by non-enforceable IVUS image acquisition owing to hemodynamic instability, incomplete imaging of stented lesion due to unreliable pullback, and unacceptable IVUS image quality. Non-VLST-experienced SES-implanted patients with serial IVUS imaging were extracted from our hospital database as the control group. Comparing IVUS images from the three VLST patients with eight control IVUS images which were taken post-stent implantation and at follow-up angiography routinely performed, morphological vessel response of SES-implanted segment was analyzed precisely. These eight control patients were monitored prospectively with documentation of the absence of any clinical adverse event during observation period and were finally selected as IVUS controls. This study was approved by the institutional review boards of the institutions in which the procedures were performed, and written informed consent was obtained from all patients.

Patient demographic data were confirmed by hospital chart review. Coronary risk factors included diabetes mellitus (diet-controlled, oral agent, or insulin-treated), hypertension (medication-treated only), dyslipidemia (medication-treated or low-density lipoprotein >140 mg/dL), cigarette smoking, and family history of coronary artery disease. Drug adherence to antiplatelet agents, which was recognized as one of the most important risk factors for VLST, was examined in detail.

IVUS image acquisition and analysis

IVUS images were acquired after intracoronary administration of nitrates using a commercially-available IVUS catheter (EagleEye™, Volcano Corp., Rancho Cordova, CA, USA; View It™, Terumo Corp., Tokyo, Japan; Atlantis SR Pro2™, Boston Scientific Corp., Natick, MA, USA). The selection of IVUS system was left to the discretion of the interventional cardiologists. At the post-stenting IVUS image acquisition, the catheter was advanced beyond the implanted stent, and was withdrawn with a motorized catheter pullback system to the extent possible. When VLST occurred, the catheter was advanced beyond the thrombosed stent after thrombectomy or small-size balloon angioplasty, and imaging was performed with a manual careful pullback as slowly as possible to the extent that the hemodynamic state remained stable. IVUS images were recorded continuously on CD-R or DVD-R for later offline analysis. Qualitative and quantitative IVUS analysis was performed by independent experienced observers (K.Y. and K.T.)

Table 1
Detailed clinical background of patients with very late stent thrombosis.

Pts. No.	Age/sex (years)	Risk factors	Target vessel	Clinical situation of SES placement	Duration from index procedure to VLST (months)	Antiplatelet therapy	Stent fracture at VLST	Stent malapposition at VLST	Peri-stent staining at follow-up CAG
1	75 M	HT/DM	LCX	NSTEMI	69	ASA (withdrawal the day before)	−	+	+
2	60 M	HT/DL	LCX	SAP	55	ASA	−	+	−
3	72 M	HT/DL	LCX	SAP	46	ASA	−	−	−
4	73 M	DM/DL	RCA	NSTEMI	29	ASA (alternate-day administration)	+	N/A	−
5[a]	62 M	HT/DL	LAD	SAP	30	ASA	−	+	+
6[a]	68F	HT/DL	LCX	UAP	50	ASA/Ticlopidine	+	−	−
7[a]	60 M	HT/DL	LCX	SAP	69	ASA	−	+	+
8	66 M	HT/DL/DM	LAD	SAP	51	None (withdrawal before one week)	−	+	+

HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery; NSTEMI, non-ST-segment elevation myocardial infarction; SAP, stable angina pectoris; UAP, unstable angina pectoris; ASA, aspirin (acetylsalicylic acid); N/A, not applicable; VLST, very late stent thrombosis; CAG, coronary angiography. Stent malapposition was defined as separation of stent struts from the arterial wall with evidence of blood flow behind the strut in the absence of a bifurcation. Peri-stent staining was defined as contrast staining outside the stent contour visually identified by angiography. Stent fracture was defined as complete or partial separation of the stent by angiography or IVUS.

[a] Three patients with very late stent thrombosis whose serial intravascular ultrasound images were obtained were Pts. No. 5, 6, and 7.

according to the criteria of American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies, and the consensus interpretation was included in the analysis [8]. With planimetry software (EchoPlaque™, INDEC Systems, Inc., Mountain View, CA, USA), quantitative IVUS analysis was performed at the proximal and distal reference segments to include external elastic membrane (EEM), stent, lumen, peri-stent plaque and media (P&M, EEM minus stent), and intimal hyperplasia (stent minus lumen) cross-sectional area (CSA). Corresponding images of post-stenting and at-VLST-onset IVUS examinations were identified by the fiduciary landmarks such as side branches, calcification, and stent edges.

Regarding the vessel response, ΔEEM and Δperi-stent P&M were calculated from the differences between post-stenting and at-VLST-onset IVUS values. Vessel expansion was defined as percentage change of EEM area [EEM at follow-up (or at-VLST-onset)/EEM at index procedure]. Peri-stent plaque expansion was defined as percent change of peri-stent P&M area [P&M at follow-up (or at-VLST-onset)/P&M at index procedure].

Statistical analysis

Statistical analysis was performed with StatView 5.0 (SAS Institute, Inc., Cary, NC, USA). Continuous variables (mean ± 1SD) were compared with unpaired Student *t* test or Mann–Whitney *U* test as appropriate according to data distribution. Categorical variables (frequencies) were compared with chi-square statistics or the Fisher exact test. A *p*-value <0.05 was considered significant.

Results

VLST onset and clinical demographics

Clinical background of all eight VLST patients is shown in Table 1. Our present analysis showed that VLST continued to occur constantly up to 6 years after SES implantation without attenuation. Regarding antiplatelet therapy, three patients had not taken the aspirin daily. In terms of mechanical disturbance of implanted stents, two patients had stent fracture documented by angiography or IVUS. In patients No. 5, No. 6, and No. 7, both post-stenting and at-VLST-onset IVUS images were obtained.

Baseline clinical characteristics were similar in patients with VLST and controls (Table 2). The situation of implanted SES (clinical presentation of acute coronary syndrome) and the other coronary risk factors (dyslipidemia, diabetes mellitus, hypertension, chronic kidney disease, and current smoking) were comparable between the groups. The stent length was similar in the two groups. Because of the blood sampling data collected during the acute phase in the VLST group, white blood cell count was significantly increased in the VLST group than in the control group.

IVUS findings

Acquired stent malapposition was more common in the VLST group than in the control group (62.5% vs. 12.5%, $p = 0.04$). Quantitative IVUS findings are summarized in Table 3. There were no differences in post-procedural IVUS images between the VLST and control groups. In follow-up IVUS images, lumen area was smaller in the VLST group than in the control group at maximal EEM area site and at minimal stent area site ($2.8 \pm 2.1\ mm^2$ vs. $7.1 \pm 3.1\ mm^2$, $p = 0.04$; $3.0 \pm 0.7\ mm^2$ vs. $5.9 \pm 2.8\ mm^2$, $p = 0.07$, respectively), probably because it was impossible to distinguish thrombus and neointima. Considering the mechanism of vessel expansion, peri-stent P&M area was significantly greater in the VLST group than in the control group ($17.8 \pm 2.7\ mm^2$ vs. $10.8 \pm 3.2\ mm^2$, $p = 0.03$). The comparison of vessel responses is summarized in Table 4. Vessel expansion ratio was significantly more accelerated in the VLST group than in the control group at stent edge (distal site 167.7 ± 32.1% vs. 101.5 ± 15.8%, $p = 0.01$, proximal site 173 ± 34.2% vs. 111.7 ± 23.0%, $p = 0.04$) and at maximum EEM area (185.6 ± 40.3% vs. 112.0 ± 12.1%, $p = 0.01$). The representative

Table 2
Clinical characteristics between patients with and without very late stent thrombosis.

	VLST Group ($n = 3$)	Control Group ($n = 8$)	*p*-Value
Age, years	63.3 ± 4.1	69.0 ± 8.7	0.3
Male sex	2 (67%)	5 (63%)	0.9
Diabetes mellitus	0 (0%)	4 (50%)	0.2
Hypertension	3 (100%)	8 (100%)	1.0
Dyslipidemia	3 (100%)	8 (100%)	1.0
Current smoking	1 (33%)	3 (38%)	0.9
Stable angina	2 (67%)	5 (63%)	0.9
Unstable angina	1 (33%)	3 (38%)	0.9
Multivessel disease	3 (100%)	5 (63%)	0.2
Left ventricular ejection fraction (%)	58.1 ± 6.39	71.4 ± 7.74	0.06
SES diameter (mm)	2.67 ± 0.29	3.03 ± 0.43	0.2
SES length (mm)	21.3 ± 5.8	22.1 ± 7.8	0.9
Follow-up duration (months)	49.7 ± 20.0	12.5 ± 4.3	<0.01
Hemoglobin A1c (%)	5.47 ± 1.17	5.98 ± 0.80	0.3
Lipid profile			
Total cholesterol (mg/dL)	166.3 ± 15.0	166.6 ± 49.3	1.0
Triglyceride (mg/dL)	113.3 ± 35.6	110.6 ± 61.1	0.9
Low-density lipoprotein cholesterol (mg/dL)	91.0 ± 18.2	93.8 ± 47.1	0.9
High-density lipoprotein cholesterol (mg/dL0	48.3 ± 11.5	57.4 ± 17.0	0.4
B-type natriuretic peptide (pg/mL)	54.2 ± 36.7	38.4 ± 33.5	0.5
Creatinine (mg/dL)	0.75 ± 0.32	0.75 ± 0.06	1.0
Estimated glomerular filtration rate (mL/min/1.73 m^2)	80.6 ± 24.2	70.9 ± 10.2	0.4
High-sensitivity C-reactive protein (mg/dL)	0.69 ± 1.06	0.05 ± 0.07	0.09
White blood cell (/μL)	10,667 ± 2054	4975 ± 1466	<0.01
Neutrophil (/μL)	6685 ± 2344	3116 ± 1406	0.01
Lymphocyte (/μL)	3294 ± 2322	1420 ± 344	0.04
Eosinocyte (/μL)	99 ± 88	101 ± 84	1.0

Data are presented as mean ± 1SD or number (%).
VLST, very late stent thrombosis; SES, sirolimus-eluting stent.

Table 3
Intravascular ultrasound measurements at post-procedure and follow-up.

	Post-procedure			Follow-up		
	VLST Group ($n=3$)	Control Group ($n=8$)	p value	VLST Group ($n=3$)	Control Group ($n=8$)	p-Value
Proximal region (1 mm proximal to proximal edge of the stent)						
EEM area (mm^2)	12.5 ± 3.3	15.5 ± 6.5	0.5	21.2 ± 3.9	16.6 ± 4.6	0.2
Lumen area (mm^2)	7.0 ± 2.8	8.0 ± 2.6	0.6	7.3 ± 2.9	8.1 ± 2.4	0.7
Minimum stent area site						
EEM area (mm^2)	10.5 ± 4.5	11.8 ± 5.0	0.5	15.9 ± 2.6	13.3 ± 4.8	0.5
Stent area (mm^2)	4.9 ± 1.7	6.1 ± 2.3	0.3	5.0 ± 1.8	6.3 ± 2.3	0.2
Lumen area (mm^2)	N/A	N/A		3.0 ± 0.7	5.9 ± 2.8	0.07
IH area (mm^2)	N/A	N/A		2.2 ± 1.5	0.6 ± 0.4	0.03
Peri-stent P&M area (mm^2)	5.6 ± 2.9	5.7 ± 2.8	0.7	10.8 ± 2.7	7.0 ± 3.4	0.04
Maximum EEM area site						
EEM area (mm^2)	13.6 ± 4.5	17.0 ± 4.9	0.4	24.2 ± 7.3	18.8 ± 4.4	0.1
Stent area (mm^2)	6.5 ± 2.4	7.6 ± 2.6	0.4	6.5 ± 5.2	7.9 ± 2.6	0.4
Lumen area (mm^2)	N/A	N/A		2.8 ± 2.1	7.1 ± 3.1	0.04
IH area (mm^2)	N/A	N/A		3.7 ± 5.2	2.3 ± 3.2	0.2
Peri-stent P&M area (mm^2)	7.1 ± 2.1	9.4 ± 3.4	0.3	17.8 ± 2.7	10.8 ± 3.2	0.03
Distal region (1 mm distal to distal edge of the stent)						
EEM area (mm^2)	10.5 ± 2.5	10.7 ± 4.2	0.9	17.2 ± 3.3	10.6 ± 3.7	0.02
Lumen area (mm^2)	6.3 ± 1.8	6.4 ± 2.4	0.9	6.8 ± 1.3	6.3 ± 3.0	0.8

Data are presented as mean ± 1SD.
VLST, very late stent thrombosis; EEM, external elastic membrane; IH, intimal hyperplasia; P&M, plaque and media; N/A, not available.

Table 4
Comparison of vessel responses between VLST and Control.

	VLST Group ($n=3$)	Control Group ($n=8$)	p-Value
Proximal region (1 mm proximal to proximal edge of the stent)			
Vessel expansion (%)	173.4 ± 34.2	111.7 ± 23.0	0.04
Minimum stent area site			
IH area (mm^2)	2.2 ± 1.5	0.6 ± 0.4	0.03
ΔEEM area (mm^2)	5.3 ± 5.5	1.4 ± 3.2	0.07
Vessel expansion (%)	174.0 ± 94.4	117.2 ± 31.9	0.2
ΔPeri-stent P&M area (mm^2)	5.2 ± 5.4	1.3 ± 3.2	0.1
Peri-stent plaque expansion (%)	271.2 ± 238.8	134.3 ± 63.2	0.2
Maximum EEM area site			
IH area (mm^2)	3.7 ± 5.2	2.3 ± 3.2	0.2
ΔEEM area (mm^2)	10.6 ± 3.4	1.7 ± 1.9	0.01
Vessel expansion (%)	185.6 ± 40.3	112.0 ± 12.1	0.01
ΔPeri-stent P&M area (mm^2)	10.6 ± 3.3	1.4 ± 1.6	0.01
Peri-stent plaque expansion (%)	262.1 ± 72.8	118.7 ± 21.2	0.01
Distal region (1 mm distal to distal edge of the stent)			
Vessel expansion (%)	167.7 ± 32.1	101.5 ± 15.8	0.01

VLST, very late stent thrombosis; IH, intimal hyperplasia.

examples of serial IVUS images of a VLST case and control case are shown in Figs. 1 and 2.

Discussion

The present study demonstrates that definite VLST occurred at a rate of 0.48%/patient and 0.39%/stent in our institution. Vascular positive remodeling occurred in the VLST group and anti-platelet therapy discontinuation may be the cause of VLST.

Epidemiology of VLST

VLST in SES occurs at a rate of 0.26–0.6%/y without attenuation and the mortality of stent thrombosis is 11–45% (including definite, possible, and probable stent thrombosis) [2,9]. When a bare metal stent (BMS) is implanted, endothelial coverage of stent struts occurs and it is the cause of restenosis. DES were created to solve this problem. Unfortunately, inflammation and hypercoagulable state occurred in DES-implanted segments by stent polymer and drugs in return for the reduction in the restenosis rate. In this study, the frequency of SES VLST was similar to that in previous studies [2,9], and it did not decrease from year to year. It may be necessary to closely follow SES-implanted patients, and to pay attention to medication adherence in these patients, especially regarding antiplatelet therapy.

Pathogenic mechanism of SES VLST and clinical implications

Using intracoronary angioscopy, Higo et al. reported that yellow color grade of neointima within SES-implanted segments increased from baseline to follow-up compared with BMS. Thrombus was detected in 25% of stent segments with yellow color grade of neointima [10]. Histopathological analysis by Cook and colleagues demonstrated that the thrombus of SES VLST showed signs of infiltrates with eosinophils. Eosinophilic infiltrates were associated with evidence of vessel remodeling, presumably leading to secondary stent malapposition [11].

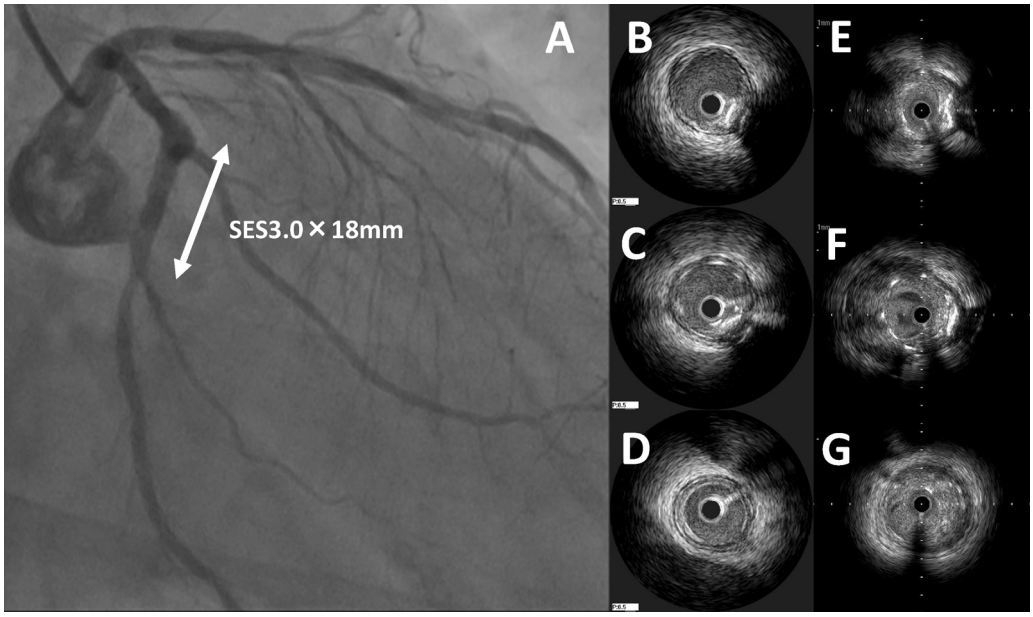

Fig. 1. Representative example of angiographic and intravascular ultrasound images in very late stent thrombosis (VLST) patient. Sirolimus-eluting stent (SES; 3.0 mm × 18 mm) had been implanted to LCX #13 on 25/6/2005. VLST occurred on 30/3/2011. He had taken aspirin daily and not experienced effort angina until the time of VLST. (A) Angiography on 18/1/2012 after 9 months of VLST. (B–D) Post-procedural stent implantation. (B) Proximal edge. (C) Stent area (D) Distal edge. (E–G) VLST. (E) Proximal edge. (F) Stent area. (G) Distal edge. External elastic membrane area: B: 16.0 mm^2 C: 18.7 mm^2 D: 13.1 mm^2 E: 25.4 mm^2 F: 26.4 mm^2 G: 20.8 mm^2.

Although the frequency of myocardial infraction and mortality were not different between the patients with SES and BMS, VLST occurs far more frequently with DES than with BMS [12]. The pathogenesis of VLST between DES and BMS was also significantly different [13]. All vasculature had not been positively remodeled and neointimal rupture was observed in all BMS VLST patients. On the other hand, positive remodeling and incomplete stent apposition occurred in SES VLST.

Our study also shows that vessel expansion was more frequent in the VLST group not only at the stented segment but also at stent edge. In case of the stent malapposition of SES or peri-stent staining on follow-up IVUS or angiography, we may have to consider close follow-up and continuing dual antiplatelet therapy for more than 1 year after SES implantation on the condition that the blood pressure is kept under control and that the patient is not at low risk for bleeding [14]. There are few reports analyzing serial IVUS images post-procedural stent implant and at the time of VLST *in vivo*. Our study showed that the vessel positive remodeling for the period from stent placement to the time of VLST and/or late stent malapposition is one of the most important morphological causes of VLST by analyzing these serial IVUS images. In terms of second-generation DES, several reports showed that neointimal coverage increased more and uncovered struts decreased more as compared with SES [15–17], and that vessel response against

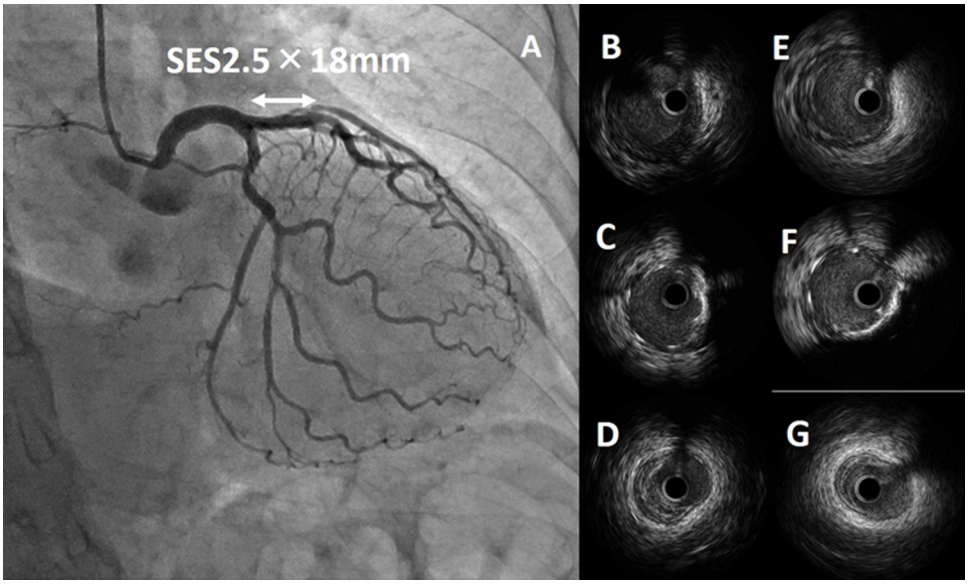

Fig. 2. Representative example of angiographic and intravascular ultrasound (IVUS) images in a control patient. Sirolimus-eluting stent (SES; 2.5 mm × 18 mm) had been implanted to left anterior descending artery #6 on 14/10/2009. Routine follow-up angiography and IVUS had been done on 4/10/2010. (A) Angiography on 4/10/2010. (B–D) Post-procedural stent implantation. (B) Proximal edge. (C) Stent area. (D) Distal edge. (E–G) Follow up on 4/10/2010. (E) Proximal edge. (F) Stent area. (G) Distal edge. External elastic membrane area: B: 12.8 mm^2 C: 17.2 mm^2 D: 9.4 mm^2 E: 14.5 mm^2 F: 22.2 mm^2 G: 8.2 mm^2.

such second-generation DES has not been fully understood, and would require future research utilizing serial coronary imaging devices.

Study limitations

This was a small, non-randomized, retrospective, and cross-sectional study performed at a single center. In our study, all eight VLST patients visited our hospital for chest pain and underwent angiography. Thus, probable or possible VLST based on ARC definition was not included in our study and probably definite VLST patients who did not visit our hospital were not included in our study. In the VLST group, IVUS images were not taken by auto pullback, and plaque volume was not analyzed. However, time-consuming auto pullback is not accepted ethically because VLST is one of the most fatal complications after stent implantation. IVUS was taken after thrombectomy or angioplasty, and neointima could not be evaluated qualitatively, and could not be clearly distinguished from thrombus. Furthermore, duration from index procedure to follow-up IVUS, which is considered to be associated with vascular response, was significantly longer in the VLST group than in the control group, and might have affected our results.

Conclusion

The positive vessel remodeling and late stent malapposition are some of the causes of SES VLST analyzed by serial IVUS images. The positive remodeling occurred not only in stented segments but also at stent edges. In addition, discontinuation of antiplatelet therapy might cause VLST.

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Conflict of interest

The authors do not have any financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this article.

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