Original Article

Underlying mechanisms of saphenous vein graft stenosis after coronary artery bypass caused by clipping of the side branches: an experimental study

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Background: Saphenous veins are regular bypass conduits selected in non-left anterior descending artery (LAD) coronary artery bypass graft (CABG) surgery. Despite the technical errors, acute thrombosis, intimal hyperplasia and arteriosclerosis which could lead to saphenous vein graft (SVG) failure, the metal-clipping-related SVG failure is unique and rare. This study was conducted to investigate the clinical and underlying mechanisms of the metal-clipping-related SVG failure.

Methods: We collected 6 typical cases of the metal-clipping-related SVG failure in 41 patients who were diagnosed graft stenosis by coronary angiograph after CABG in the Department of Cardiology, Beijing Anzhen Hospital, from January 2020 to September 2021. Furthermore, we built an *in vitro* model to verify the identical intravascular ultrasound (IVUS) pattern of metal clip.

Results: There were 6 in 41 cases of SVG stenosis caused by clipping of the side branches. We found that the stenosis of SVG caused by metal clipping mostly occurred at the corner and multipole clipping points. In this situation, great resistance could be felt when pushing the instruments through the stenosis and crystallized cholesterol was rarely caught by the distal protection device. We verified the similar IVUS pattern of metal clip at the side-branches of SVG *in vitro*.

Conclusions: The metal-clipping-related stenosis may lead to SVG failure. The stenosis of SVG caused by metal clipping mostly occurred at the corner and multipole clipping points. IVUS showed great modality for clarification.

Keywords: Saphenous vein graft stenosis (SVG stenosis); coronary artery bypass (CABG); intravascular ultrasonography (IVUS); drug-eluting balloon (DEB)

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Introduction

Saphenous veins are regular bypass conduits selected in non-left anterior descending artery (LAD) coronary artery bypass graft (CABG) surgery. Graft stenosis of the saphenous vein may be associated with poor outcomes for CABG. Saphenous vein graft (SVG) occlusion occurs at a rate of approximately of 2–3% per year, and at a rate of approximately 4% 6–10 years after CABG (1). The mechanism of SVG atherosclerosis after CABG has been well documented (2,3). Despite the technical errors, acute

Table 1 Clinical manifestations of patients

No.	Gender	Age	Hypertension	Dyslipidemia	Diabetes	Antiplatelet drugs	Statin	History of CABG (y)
1	F	75	√	√	√	√	√	5
2	F	67	√	√		√	√	6
3	F	64	√	√		√	√	11
4	M	82	√	√	√	√	√	18
5	M	67	√	√			√	10
6	F	64		√	√	√	√	4

CABG, coronary angiography bypass graft.

thrombosis, intimal hyperplasia during the first year of CABG failure and the SVG arteriosclerosis during the late failure, the mechanism of clipping related late SVG stenosis is unique. The clinical and Intravascular ultrasound (IVUS) views of SVG stenosis caused by clipping of side-branches have rarely been reported. This study was conducted to investigate the clinical and IVUS characteristics of SVG stenosis caused by clipping of side-branches. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-235/rc).

Methods

Research design

This is an experimental study included the *in vivo* and *in vitro*. *In vivo*, we collected 41 patients who underwent coronary angiography (CA) after CABG in the Department of Cardiology, Beijing Anzhen Hospital, from January 2020 to September 2021. There were six cases of SVG stenosis caused by the clipping of the side branches. Furthermore, we built an *in vitro* model to verify the identical IVUS pattern of metal clip in the cases above. While imitating the regular operation of SVG anastomosis, we performed traditional harvesting method with a single ligation and a metal clip.

Clinical characteristics were collected using the computerized patient record system at our hospital. The SVGs used in the *in vitro* model were collected from residual saphenous veins after grafts had been conducted according to routine surgical processes. All the grafts were collected with written informed consent from the Department of Cardiac Surgery, Beijing Anzhen Hospital. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and approved by the Clinical Research Ethics Board of Beijing Anzhen Hospital, Capital Medical University (No. 2021010X).

IVUS inspection: an IVUS system (Boston Scientific OptiCross^{TM}; Marlborough, MA, USA) was performed with a frequency of 60 MHz. An intracoronary nitroglycerin was administered before IVUS was drawn back. The ultrasound catheter was retracted at a constant speed (at 0.5–1 mm per second).

Statistical analysis

The baseline characteristics of patients such as the postoperative time of CABG were presented as mean ± SD for continuous variables. Categorical variables were presented as percentage. Statistical analyses were performed with SPSS statistics, version 20.0 (IBM Corporation, NY, USA). The clinical manifestations, medical history and treatment processes of each patient were documented in the *Table 1*.

Results

Clinical and imaging materials of six typical cases (14.6%) of diagnosed SVG stenosis caused by metal clipping were analyzed in this study. The average age of the patients was 69.83±7.195 years. The average postoperative time of CABG was 9±5.215 years. Their clinical manifestations, past medical history, and treatment processes are described in *Table 1*.

Case 1, a 75-year-old Chinese male (with hypertension, dyslipidemia, type-2 diabetes, and a history of inferior myocardial infarction) presented with recurrent exertional chest pain for 5 years following CABG surgery. The patient's grafts included: left internal mammary artery (LIMA) → LAD, and aorta → SVG → diagonal branch → right

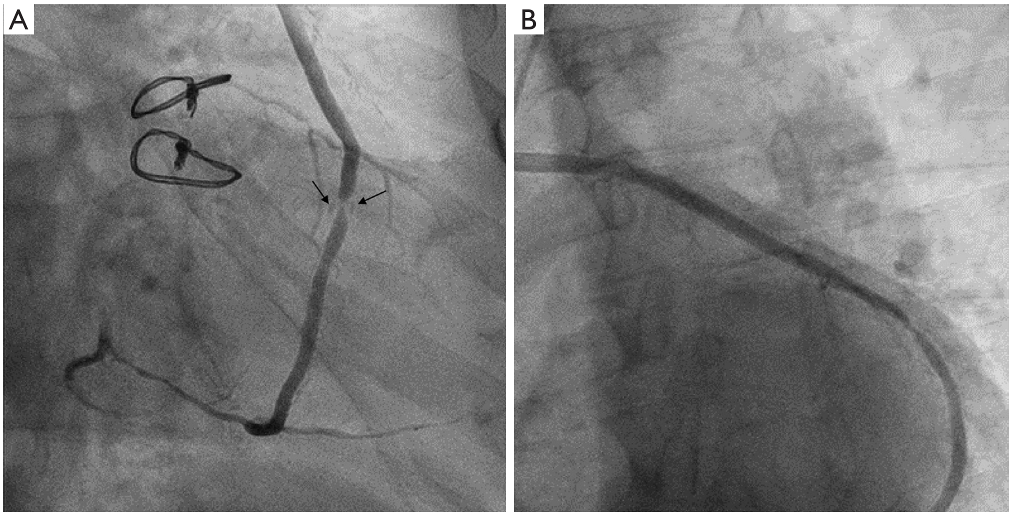

Figure 1 Coronary angiography showing stenosis at the mid-portion of the SVG. The images of coronary angiography demonstrating SVG from anterior-posterior view (A) and right anterior oblique view (B). The arrows suggest the location of the clipping of side-branches. SVG, saphenous vein graft.

coronary artery (RCA). His regular medication included aspirin, metoprolol, rosuvastatin, and metformin after the CABG. The CA showed stenosis at the mid-portion of the SVG (see *Figure 1*). An IVUS (Boston Scientific OptiCross^{TM}; Marlborough, MA, USA) was performed at the SVG stenosis and the clipping of side-branches were observed at the side of stenosis (see *Figure 2*). Due to the rare signs of neo-arteriosclerosis and the unsatisfied immediate effect after pre-dilatation with non-compliant balloon (Boston Scientific Quantum 3.5 mm × 15 mm; Boston Scientific, USA), a drug-coated balloon (DCB; Bingo, 3.5 mm × 15 mm, Yinyi Biotech, Dalian, China) was used instead of a drug eluting stent (DES) without the distal protection device (*Figure 3*).

Case 2, a 67-year-old female with hypertension and dyslipidemia was diagnosed with stable angina at 6 years from CABG. The CA showed acceptable patency in the LIMA and a stenosis at the proximal segment of SVG to the left circumflex coronary (*Figure 4*). The IVUS showed neo-arteriosclerosis at the proximal segment of the SVG (*Figure 4C*) and different signs of stenosis caused by clipping of side-branches in the middle segment of the SVG (*Figure 4B*). A percutaneous coronary intervention (PCI) was performed using a distal protection device, and a drug-eluting stent (TIVOLI 3.0 mm × 15 mm, Essen Technology Beijing Co. Ltd., Beijing, China) was implanted (*Figure 5*).

Case 3, a 64-year-old female with hypertension and dyslipidemia was diagnosed with unstable angina 1 week after CABG. The patient's grafts included: LIMA → LAD, aorta → SVG → diagonal branch → obtuse marginal branch → posterior descending branch. Aspirin, clopidogrel, and atorvastatin were regularly prescribed. The CA showed the stenosis in SVG from the diagonal branch to the obtuse marginal branch was partly caused by 2 metal clippings. When the instruments such as the distal protection device and the drug-eluting stent (Medtronic Resolute Integrity 3.0 mm × 18 mm, Medtronic, Dublin, Ireland) were pushed through the stenosis caused by metal clipping, rough resistance could be felt (*Figure 6*).

Case 4, an 82-year-old male with hypertension, type 2 diabetes, and dyslipidemia was diagnosed with stable angina for 2 years following 18-year CABG. The patient's grafts were as follows: LIMA → LAD, aorta → SVG → obtuse marginal branch, aorta → SVG → posterior descending branch. The patient had continually taken aspirin and rosuvastatin since the CABG 18 years ago. The CA showed 3 metal clipping in the stenosis of SVG from aorta to posterior descending branch (*Figure 7*).

Case 5, a 67-year-old male (with hypertension, dyslipidemia, and a history of inferior myocardial infarction) experienced atypical chest pain after 10 years CABG. The patient had regularly taken statin. The patient's grafts were as follows: LIMA → LAD, aorta → SVG → OM → PDA. The CA and the coronary computed scan showed mild

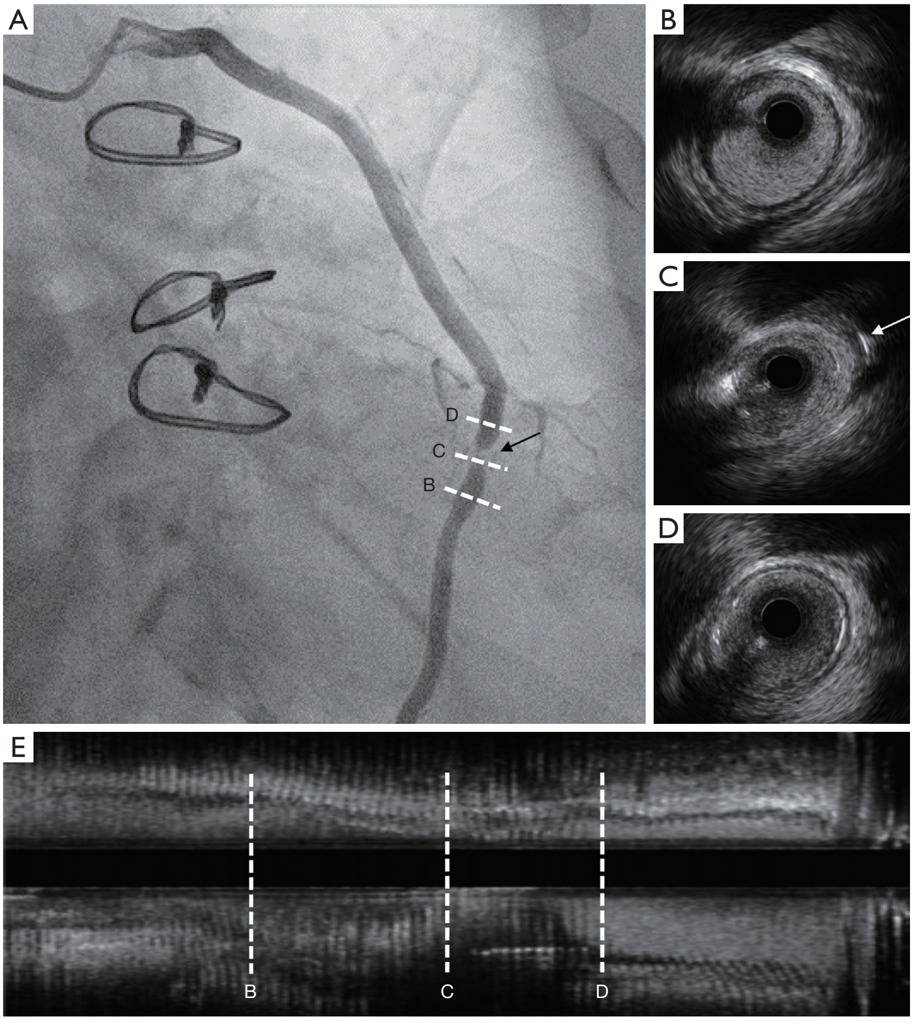

Figure 2 The IVUS images of case 1 SVG in the proximal (D), stenotic (C), and distal sites (B). (A) The image of coronary angiography demonstrating SVG. (E) The long axis of IVUS image of SVG obtained by regular pullback from the distant segment. The arrows suggest the location of the clipping of side-branches. IVUS, intravascular ultrasound; SVG, saphenous vein graft.

stenosis at the SVG which was caused by the metal clipping (*Figure 8*).

Case 6, a 64-year-old female with type 2 diabetes, dyslipidemia, and a history of inferior myocardial infarction was diagnosed with unstable angina 4 years after CABG. She had regularly taken dual antiplatelet drugs and rosuvastatin. The patient's grafts were as follows: LIMA → LAD, aorta → SVG → diagonal branch → obtuse marginal branch → posterior descending branch. The CA showed the stenosis at the proximal of the SVG caused by the metal clipping. Vascular dissection occurred after non-compliant balloon pre-dilatation (Boston Scientific Quantum Maverick 3.5 mm × 20 mm); therefore, a drug-eluting stent (Medtronic Resolute Integrity 4.0 mm × 22 mm) was implanted (*Figure 9*).

IVUS image of SVGs in vitro

Images of IVUS performed in both intact and longitudinally incised SVG were demonstrated (*Figure 10*). Similar patterns of IVUS images in the *in vitro* model showed the SVG failures in the cases above were mainly caused by the metal clip.

Discussion

In our research, we found that 6 of 41 patients occurred

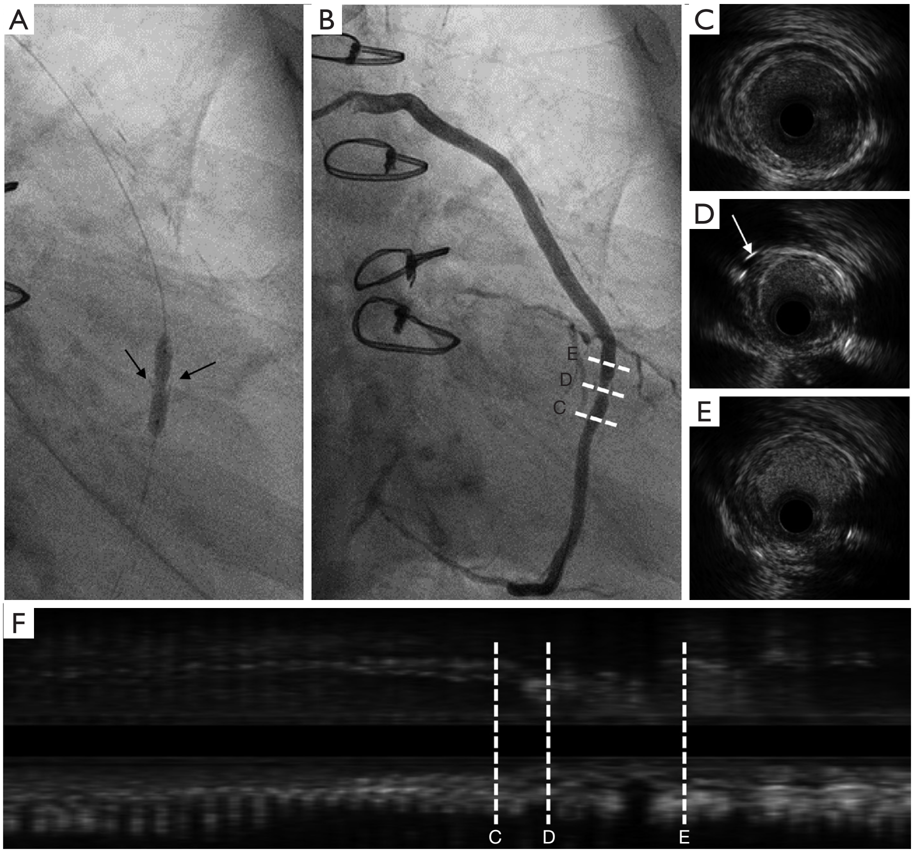

Figure 3 The IVUS images obtained after the dilatation of DCB of case 1 SVG in the proximal (E), stenotic (D), and distal sites (C). (A) The image of coronary angiography demonstrating the dilatation of non-compliant balloon. (B) The image of coronary angiography demonstrating the unsatisfied immediate effect after dilatation with DCB. (F) The long axis of IVUS image of SVG obtained by regular pullback from the distant segment after the dilatation of DCB. The arrows were suggesting the location of the clipping of side-branches. IVUS, intravascular ultrasound; DCB, drug-coated balloon; SVG, saphenous vein graft.

metal-clipping-related late SVG failure. The stenosis of SVG caused by metal clipping mostly occurred at the corner and multipole clipping points. In this situation, great resistance could be felt when pushing the instruments through the stenosis and crystallized cholesterol was rarely caught by the distal protection device.

The number of CABG operated has been increasing at a rate of 10% annually in China, reaching 45,455 in 2017 (4). Although internal thoracic artery, radial artery, and gastroepiploic artery have become optional graft locations, the SVG remains the most widely used non-LAD bypass conduit due to its accessibility, although without satisfactory longevity and durability (5). Previous studies have indicated that 10–20% of SVGs fail in 1 year after the procedures (6,7). An additional 5–10% of SVGs fail in the 1–5 years after CABG and the proportion reaches 20–25% in 6–10 years (8). Patency at 10 years is only about 60% for SVGs (9).

The mechanism of SVG failure after CABG has been extensively discussed. Technical errors, acute thrombosis, and intimal hyperplasia are the main cause of SVG failure during the first year after CABG (10). Furthermore, late failure occurs due to SVG arteriosclerosis (10). Advanced endovascular imaging technology sheds light on the potential mechanisms and physiology of SVG failure progression, such as twisted SVG leading to acute mechanical stenosis (11), and "upside down" venous valve leading to late SVG stenosis following 12-year-CABG (12). The cases above demonstrated another mechanism that led to the SVG failure. This report is the first IVUS documentation of the late SVG stenosis caused by clipping of side-branches. Metal-clipping-related SVGs failure may improve the understanding of the pathophysiology of

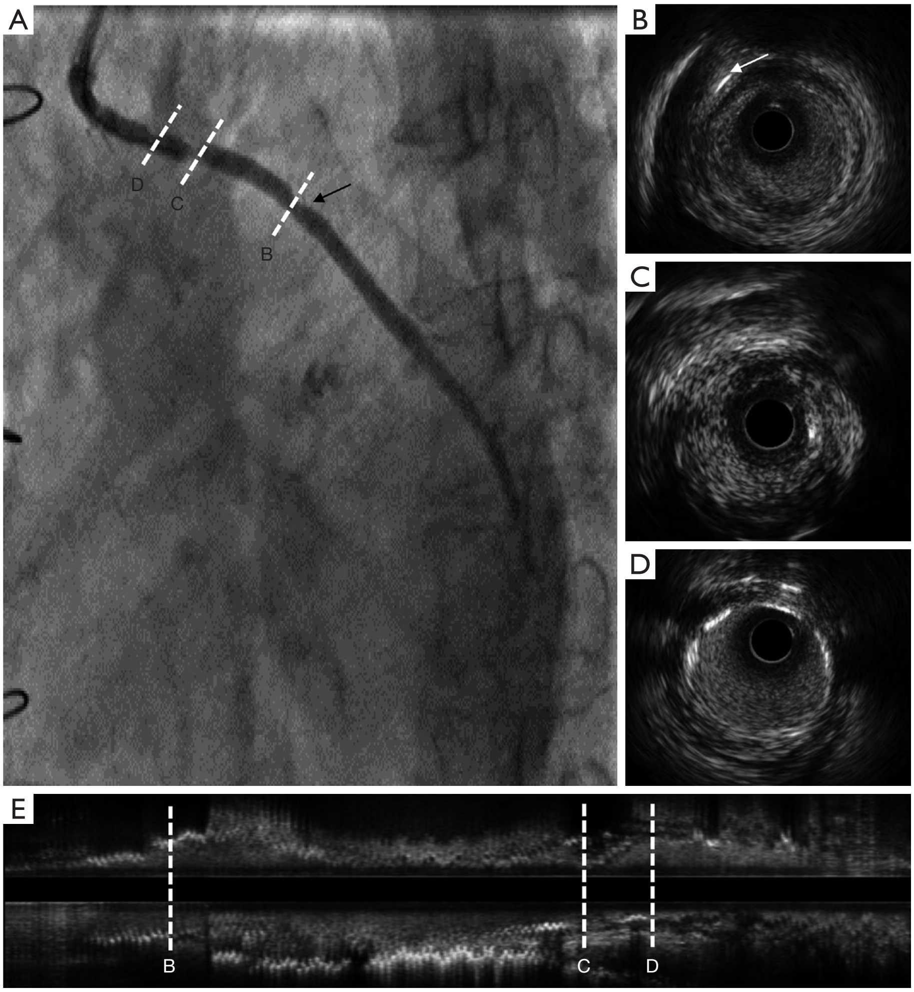

Figure 4 A 67-year-old female with hypertension and dyslipidemia was diagnosed with stable angina 6 years after the CABG. An angiography shows suitable patency in LIMA and stenosis at the proximal segment of SVG to the left circumflex coronary (A). An IVUS showing neo-arteriosclerosis at the proximal segment of the SVG, and the stenosis in the middle segment of the SVG shows clipping of the side branches (B-E). The arrows were suggesting the location of the metal clipping of side-branches. CABG, coronary artery bypass graft; LIMA, left internal mammary artery; SVG, saphenous vein graft; IVUS, intravascular ultrasound.

venous graft failure. Surgical manipulation of preparation and technology of harvesting may play a critical role in long-term SVG patency (13). Mechanical force by either clipping or ligation may lead to iatrogenic injury of SVG structure. A previous study showed that mechanical shrinkage of clipped side branches affects the layers of adjacent SVG segments (14). Sanisoglu *et al.* reported that compared to ligation, clipping the side-branches of the SVG during its harvesting for coronary bypass grafting is associated with decreased vein damage (14). Not only the external stent (15), but also the "no-touch" technique (16) is associated with reduced SVG patency.

Limitations

Unfortunately, research documenting the phenomenon of metal-clipping-related late SVG failure is scarce. In our study we reported that 6 of 41 patients occurred metal-clipping-related late SVG failure. But the limitation of study is that the sample of study is too small to assess the incidence rate of metal-clipping-related late SVG failure. Large-scale clinical research for further exploring was required.

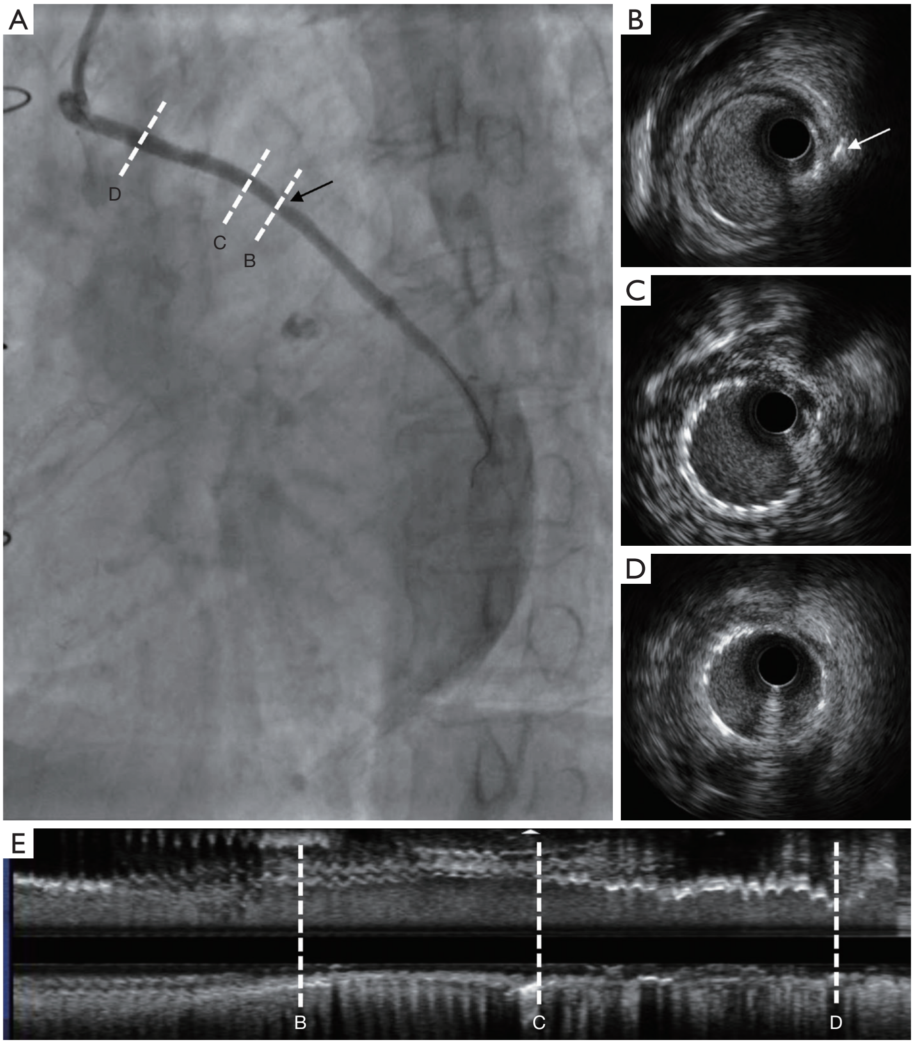

Figure 5 The IVUS images obtained after the implantation of DES of case 2 SVG in the proximal (D), stenotic (C), and distal sites (B). (A) The image of coronary angiography demonstrating the immediate effect after implantation of DES. (E) The long axis of IVUS image of SVG obtained by regular pullback from the distant segment after the dilatation of DCB. The arrows were suggesting the location of the clipping of side-branches. IVUS, intravascular ultrasound; DES, drug-eluting stent; SVG, saphenous vein graft; DCB, drug-coated balloon.

Conclusions

Our study indicated that IVUS is a very useful modality for clarification of the SVG stenosis caused by clipping of side-branches, as it sheds lights on the potential mechanisms and physiology of late SVG progression failure.

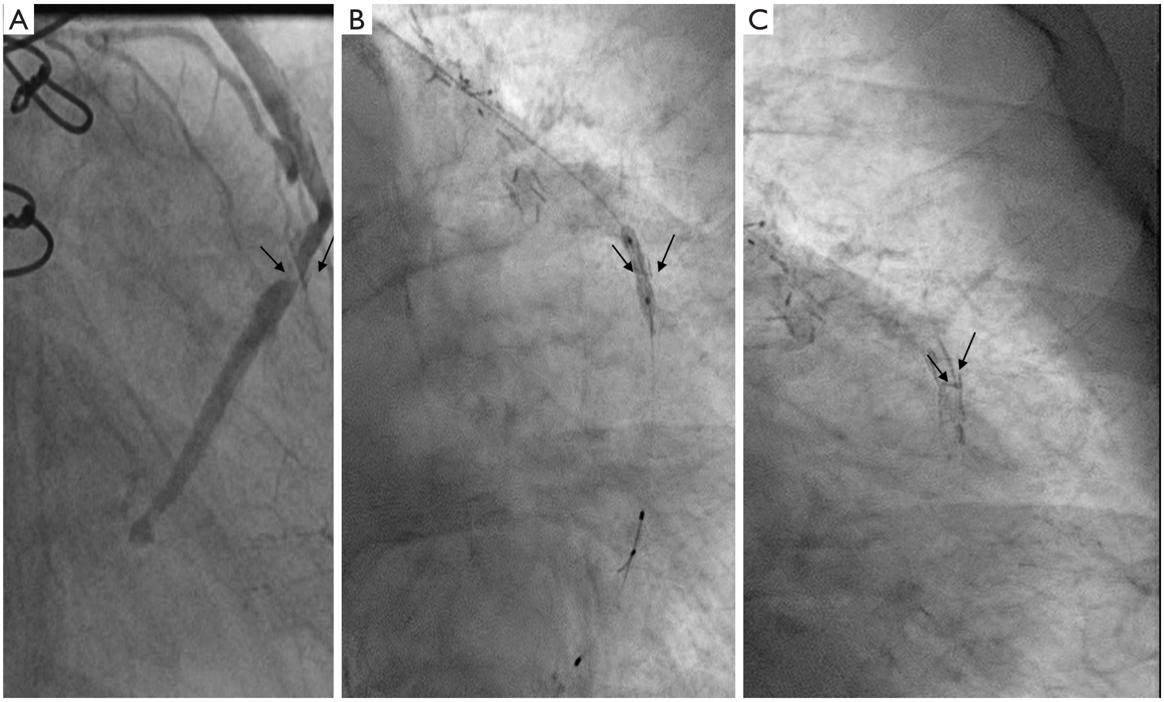

Figure 6 Coronary angiography showing stenosis in the SVG caused by 2 metal clippings (A,B). The stenosis which existed metal clipping caused great resistance when pushing the instruments (C). The arrows were suggesting the location of the clipping of side-branches. SVG, saphenous vein graft.

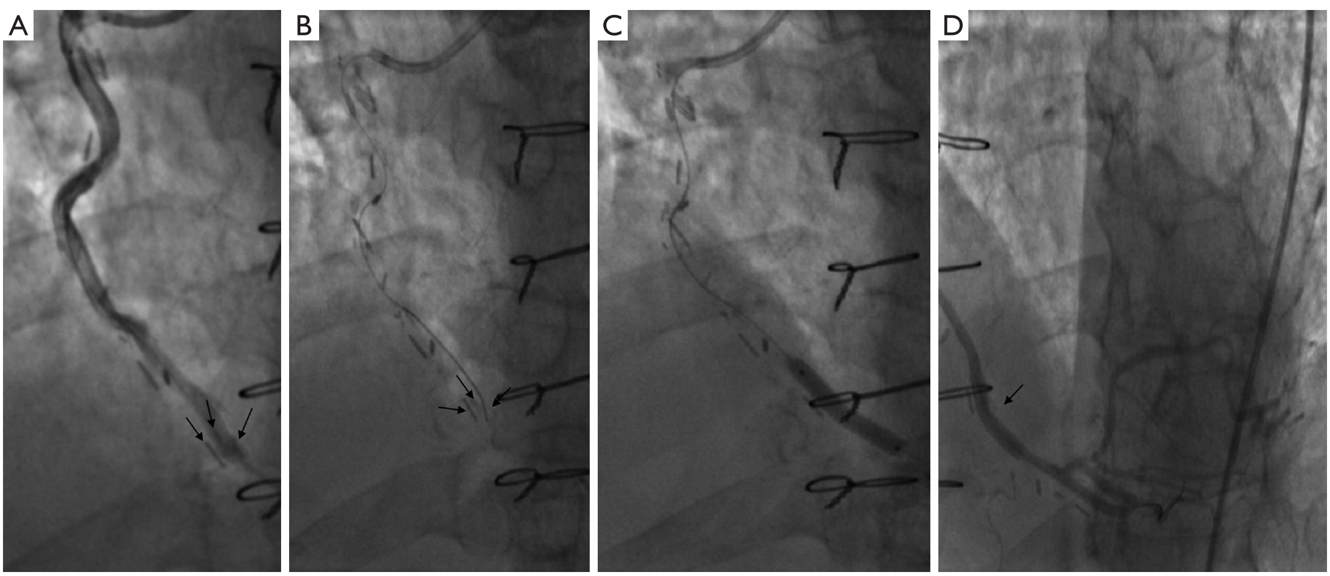

Figure 7 An 82-year-old male with stenosis in the distal of SVG caused by 3 metal clippings (A-D). The arrows were suggesting the location of the 3 metal clipping of side-branches. SVG, saphenous vein graft.

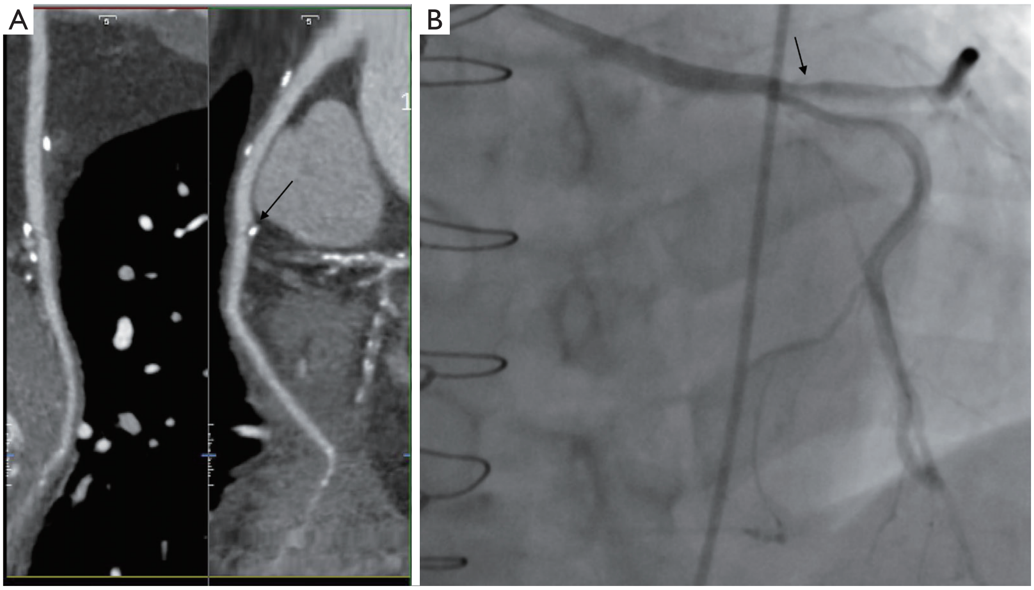

Figure 8 The coronary angiography (B) and the CT scan (A) showing the early stage of stenosis at the SVG. The arrows were suggesting the location of the clipping of side-branches. CT, computed tomography; SVG, saphenous vein graft.

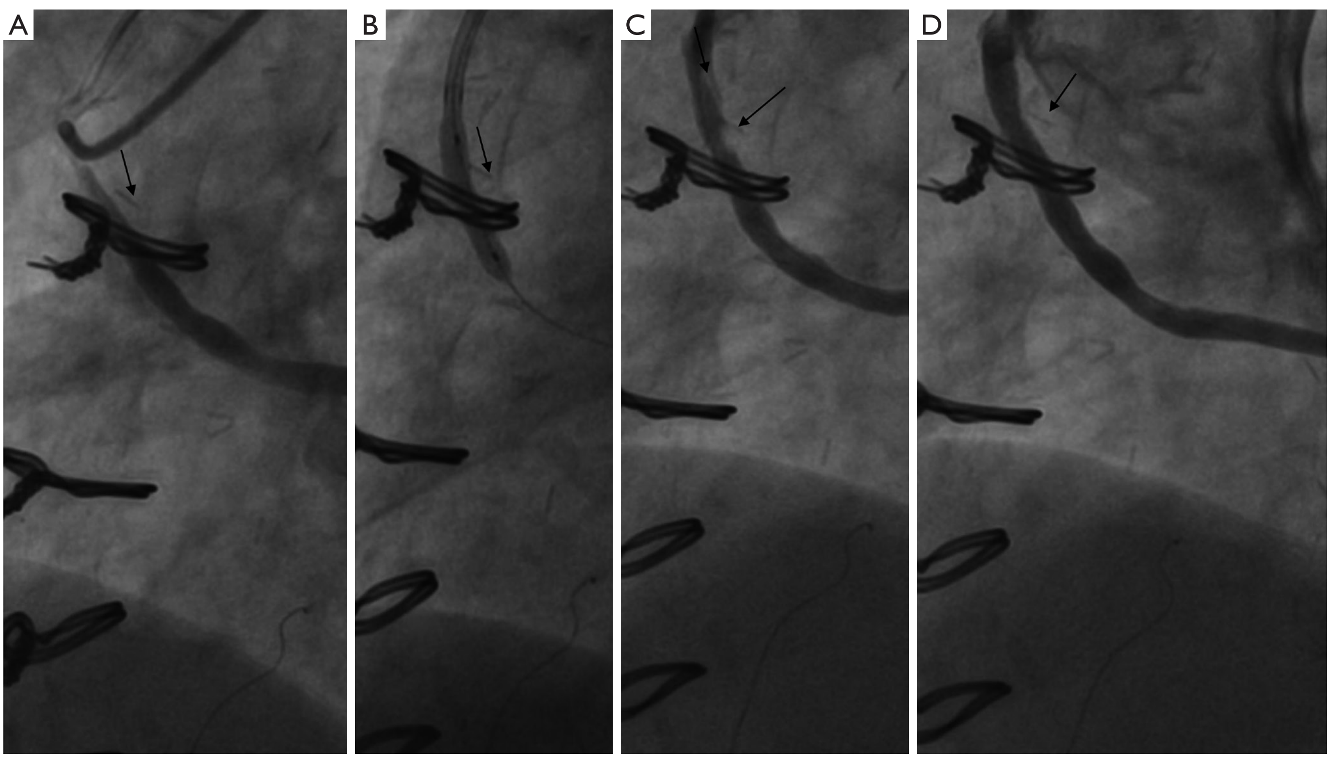

Figure 9 Vascular dissection occurred after non-compliant balloon dilatation (A-C), a drug-eluting stent was implanted (D). The arrows were suggesting the location of the clipping of side-branches.

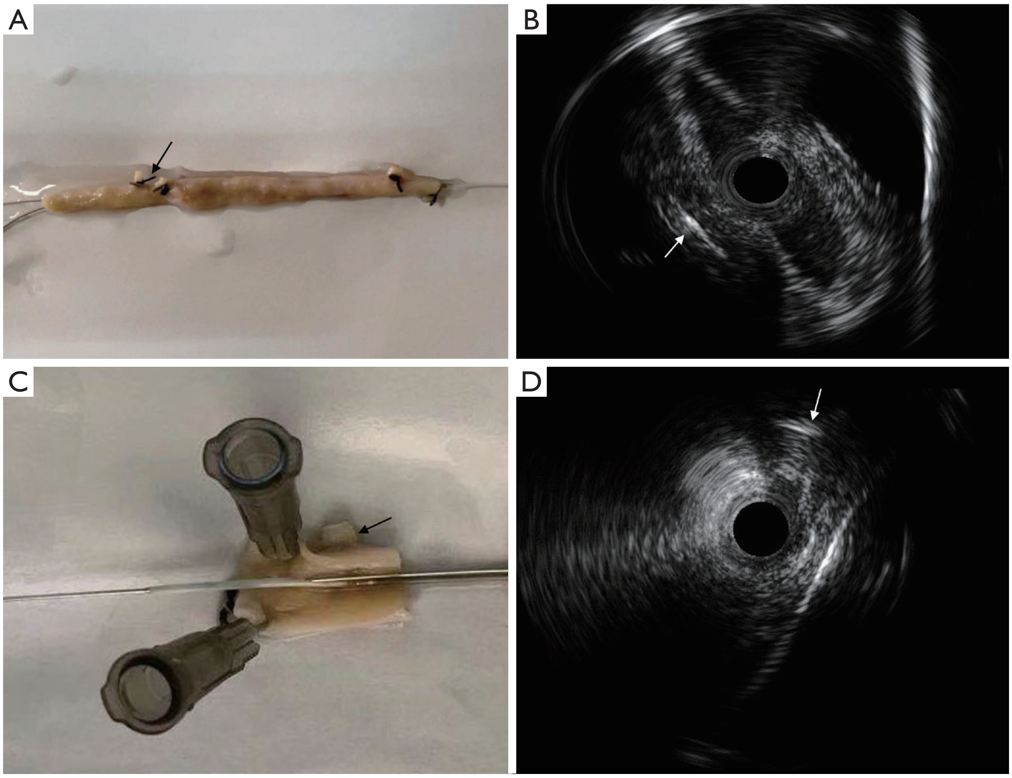

Figure 10 Imitating the regular operation of SVG anastomosis, we established a model (A) and incised it longitudinally (C). Images of IVUS performed in both intact (B) and longitudinally incised SVG (D) were demonstrated. The arrows suggest the location of the clipping of side-branches. SVG, saphenous vein graft; IVUS, intravascular ultrasound.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-235/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-235/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-235/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and approved by the Clinical Research Ethics Board of Beijing Anzhen Hospital, Capital Medical University (No. 2021010X) and informed consent was taken from all the patients.

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