Application of virtual histological intravascular ultrasound in plaque composition assessment of saphenous vein graft diseases

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Abstract

Objective: Saphenous vein grafts disease (SVGD) is a common complication after coronary artery bypass graft (CABG) and normally treated by percutaneous coronary intervention (PCI). The most common complication after SVG-PCI is slow or no-reflow. It is known that the no-reflow phenomenon occurs in up to 15% of the SVG-PCI and is associated with high risk of major adverse cardiac events (MACEs) and mortality, therefore, it is important to investigate the factors that could predict the clinical outcome of PCI for risk stratification and guiding interventions. In recent years, the spectral analysis of intravascular ultrasound (IVUS) radiofrequency data (virtual histology-IVUS [VH-IVUS]) has been used to provide quantitative assessment on both plaque compositions and morphologic characteristics.

Data sources: The PubMed, Embase, and Central databases were searched for possible relevant studies published from 1997 to 2018 using the following index keywords: "Coronary artery bypass grafting," "Saphenous venous graft disease," "Virtual histology-intravascular ultrasound," "Virtual histology-intravascular ultrasound," and "Percutaneous coronary intervention."

Study selection: The primary references were Chinese and English articles including original studies and literature reviews, were identified and reviewed to summarize the advances in the application of VH-IVUS techniques *in situ* vascular and venous graft vascular lesions.

Results: With different plaque components exhibiting a defined spectrum, VH-IVUS can classify atherosclerotic plaque into four types: fibrous tissue (FT), fibro fatty (FF), necrotic core (NC), and dense calcium (DC). The radiofrequency signal is mathematically transformed into a color-coded representation, including lipid, fibrous tissue, calcification, and necrotic core. Several studies have demonstrated the independent relationship between VH-IVUS–defined plaque classification or plaque composition and MACEs, but a significant association between plaque components and no-reflow after PCI in acute coronary syndrome. In recent years, VH-IVUS are applied to assess the plaque composition of SVGD, based on the similarity of pathophysiological mechanisms between coronary artery disease (CAD) and SVGD, further studies with the larger sample size, the long-term follow-up, multicenter clinical trials may be warranted to investigate the relationship between plaque composition of saphenous vein graft (SVG) by VH-IVUS and clinical outcomes in patients with SVGD undergoing PCI.

Conclusions: In degenerative SVG lesions, VH-IVUS found that plaque composition was associated with clinical features, future studies need to explore the relationship between VH-IVUS defined atherosclerotic plaque components and clinical outcomes in SVGD patients undergoing PCI, an innovative prediction tool of clinical outcomes can be created.

Keywords: Coronary artery bypass grafting; Saphenous venous graft disease; Virtual histology-intravascular ultrasound; Percutaneous coronary intervention

Introduction

Coronary artery bypass grafting (CABG) is a major method of surgical treatment for coronary artery disease (CAD). The number of CABG procedures performed has exceeded 40,000, increased at a rate of 10% annually in China, which is notable given the CABG caseload (47,207 in 2016).[1] Saphenous vein grafts (SVGs) are commonly used in CABG due to the advantage of availability, although the patency rates of SVGs are lower than that for arterial grafts.[2,3] However, declining SVG patency rates (from 93% at 1 year to 41% at 10 years) due to degenerative and/or occlusive disease (SVG disease [SVGD]: symptomatic ≥50% stenosis in at least one

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SVG[2]) seriously limit the long-term efficacy of CABG.[4] Newly developed atherosclerosis is the major reason for long-term poor prognosis,[3] SVGD has become an important cause of morbidity and mortality for CAD patients after CABG surgery.[5,6] Prediction of clinical outcome, treatment, and prevention of SVGD remain challenging.

SVGD revascularization could be achieved with redo-CABG surgery or percutaneous coronary intervention (PCI). PCI is currently the preferred revascularization strategy in the treatment of SVGD, because redo-CABG is associated with an increased morbidity and mortality.[7-9] However, because of accelerated intimal proliferation and hyperplasia in venous conduits, SVG-PCI is associated with increased risk of late failure and worse outcomes compared with native coronary artery interventions.[10,11] The most common complication after PCI is slow or no-reflow. It is known that the no-reflow phenomenon occurs in up to 15% of the SVG-PCI and is associated with high risk of major adverse cardiac events (MACEs) and mortality.[12,13] Currently, the success in the management of no-reflow phenomenon after SVG-PCI is limited.[14] Previous studies have shown that the incidence of MACEs in patients who undergo bypass-graft PCI is significantly higher than that in patients with native coronary artery PCI,[15,16] therefore, it is important to investigate the factors that could predict the clinical outcome of SVG-PCI for risk stratification and guiding interventions.

Gray-scale intravascular ultrasound (IVUS) has been used to identify vulnerable atherosclerotic plaques with a high risk of coronary events. Plaque characteristics such as plaque burden, multiple plaque ruptures, lipid pool-like image, and minimum luminal area (MLA) were found associated with no-reflow phenomenon after PCI.[17-20] In recent years, the spectral analysis of IVUS radiofrequency data (Virtual histology-IVUS [VH-IVUS]) has been used to provide quantitative assessment on both plaque compositions and morphologic characteristics. Several studies have demonstrated that there was an independent relationship between VH-IVUS–defined plaque classification or plaque composition and MACE,[21,22] but a significant association between plaque components and no-reflow after PCI in acute coronary syndrome (ACS).[23-28] Considering similar pathophysiological mechanisms for CAD and SVGD and morphological instability of the SVG plaques, it is critically important to investigate the relationship between plaque composition of SVG by VH-IVUS and clinical outcome in SVGD patients undergoing PCI, which could identify morphologic features that are predictive of post-PCI MACEs.

Basic Principles and Advantages of VH-IVUS

IVUS requires the delivery of micro-ultrasound transducers to the lumen of coronary arteries and allows cross-sectional images of the target blood vessel to be displayed by an electronic imaging system in the ultrasound conduit. Compared with pathohistological assessments, the ability of traditional gray-scale IVUS to precisely interpret and predict the components of atherosclerotic plaques is limited. Based on the traditional gray-scale IVUS, clinically applied IVUS radiofrequency signal analysis methods mainly have three modes: VH-IVUS, iMap^{TM} IVUS (Boston), integrated backscatter IVUS (IB-IVUS), all new post-processing technology, through the processing of power spectrum for comparative analysis, through the operation of different echo frequencies of different tissues, simulation imaging, and quantitative analysis of plaque tissue components.

VH-IVUS is the most widely used in clinical practice, is a new intravascular imaging technology for atherosclerotic plaques that has emerged in recent years, VH-IVUS analyzes spectrum signals in the echo and recognizes the distinct echo frequencies of different coronary atherosclerotic tissues. This allows the construction of a colorized tissue map of plaque composition, which leads to more precise qualitative and quantitative analysis of atherosclerotic plaques and improved interventional therapy. On the basis of radiofrequency IVUS, VH-IVUS plaque components and morphology are classified into the following four types: fibrous tissue (FT), fibro fatty (FF), necrotic core (NC), and dense calcium (DC).[29,30] The reported VH-IVUS recognizes the sensitivity and specificity of lipid-rich NC 91.7% and 96.6%.[31] IB-IVUS can also obtain detailed plaque composition information, which is accurate for the identification of FT, FF and DC 92%, 91%, and 95%; [32] the sensitivity of detecting lipid plaques *in vitro* is 90%, and the specificity is 92%.[33]

Currently, gray-scale IVUS still dominates and is used as a basic criterion for evaluating other emerging devices and technologies during interventional procedures [Table 1]. However, the resolution of gray-scale IVUS is low, and the

Table 1: Comparison of advantages and disadvantages of various intravascular imaging techniques.

Items	IVUS (40 MHz)	VH-IVUS (20 MHz)	OCT	NIRS	Angioscopy	MR angiography
Axial resolution	100	200	10	NA	10–50	250–300
Stent expansion and detection of PCI complications	++	±	+	−	±	−
NC determine	±	+	+	++	+	++
Identify TCFA	−	++	++	±	+	+
Embolic detection	±	−	+	−	++	+
Stent apposition	+	+	++	−	++	−

++: very good; +: good; ±: may be valid; −: invalid. IVUS: Intravascular ultrasound; MR: Magnetic resonance; NA: Not available; NIRS: Near infrared spectrum instrument; OCT: Optical coherence tomography; TCFA: Thin-cap fibroatheroma; VH-IVUS: Virtual histology intravascular ultrasound.

nature of plaque is unclear. VH-IVUS can identify plaque composition, especially for lipid-rich NC, but VH-IVUS does not recognize the rate of thrombus as gray-scale IVUS, and cannot make a good judgment on the plaque composition after calcification. Angiography is currently the most reliable means of diagnosing red and white blood clots. With the highest spatial resolution, optical coherence tomography (OCT) has emerged as an important imaging modality for intracoronary evaluation.[34] The direct comparison between VH-IVUS and OCT by Brown *et al*[35] found that both VH-IVUS and OCT could identify advanced coronary plaques and that combined VH-IVUS/OCT was better than either alone. However, OCT has a low signal penetration through lipid or NC, and cannot adequately acquire images of the whole vessels with large lumen diameter or large NC.[36,37] This presents a problem for imaging of large vessels including vein grafts. The presence of macrophages, foam cells, microcalcifications, or hemosiderin, often co-existent with the NC, could be adverse to accurate OCT assessment of lipidic plaque.[36,37] Near-infrared spectroscopy and intravascular MRI can better discriminate lipids, especially superficial lipid cores.

Application of VH-IVUS in the Assessment of Plaque Composition of SVGD

SVGD is a complex and dynamic process. Following surgical implantation, SVG catheters undergo a series of histological and morphological alterations caused by exposure to systemic arterial pressure. It has been found that 10% to 25% of SVG patients develop thrombosis 1 year post-surgery.[38,39] The earliest reported atherosclerosis in SVG was approximately 1 year after surgery and NC were observed 2 to 5 years after surgery. Intraluminal hemorrhage was observed over 5 years following SVG surgery because of expansion of the NC.[40,41] About 7 years after surgical intervention, the histological composition of atherosclerotic plaques in patients with SVG was identical to that in native coronary arteries.[42] Castagna *et al*[43] used IVUS to analyze plaques in SVGs. They found that, in contrast to autologous vascular plaques with rich calcification, calcification in SVGs was sparse and mostly distributed in the blood vessel wall rather than within the plaque. The NC inside the plaque was rich in fats, making the plaque sparse and floppy. The fibrous caps were thin or even absent. In conjunction with the high mechanical stress from outside the plaque, the risk of rupture in fragile areas of the plaque increased and distal embolization was likely to occur, leading to no-reflow and perioperative myocardial infarction.Wang *et al*[44] used serial IVUS to assess changes in SVG morphology by measuring vessel, lumen, and plaque (vessel minus lumen) areas in corresponding IVUS cross-sectional images at 9 months, 24 months, and 6 years after CABG, they found there were minimal changes from 9 months to 6 years, lumen decrease because of negative remodeling, lumen increase was because of positive remodeling with minimum plaque progression.

Wood *et al*[45] pioneered the use of VH-IVUS to analyze the composition of SVG and demonstrated the feasibility of using VH-IVUS in SVG assessment. In their study, involving 16 cases of SVG (10 anastomotic lesions and six individual lesions), they recorded lumen area, plaque volume, reconstruction index and histological parameters of VH-IVUS. The study found that: SVG was mainly composed of FT ($50 \pm 12\%$); there was no significant difference between body and anastomotic lesions (48 ± 16 *vs.* 50 ± 8 mm, $P = 0.7$) and the duration of SVG was irrelevant to the four histological subtypes analyzed by VH-IVUS. Komatsu *et al*[46] employed VH-IVUS to analyze a patient with severe stenosis in the mid-segment of the left circumflex coronary artery (LCX). The study showed that the plaque had 16% NC and 36% of FF. Jim *et al*[47] characterized SVG lesions using VH-IVUS and were able to correlate plaque compositions with lesion characteristics. In this study, 38 patients with SVG were recruited for VH-IVUS and images were collected and measured at the smallest lumen. A total of 54 SVG lesions were analyzed. Statistical analyses were performed on single-factor clinical variables, including graft duration, diabetes, lesion lumen area, minimum lumen diameter, plaque area, and plaque burden, together with IVUS parameters. Plaque burden was shown to be positively correlated with remodeling index ($r = 0.37$, $P = 0.01$) and the percentage of FF ($r = 0.49$, $P < 0.001$), but negatively correlated with DC. Lesions with plaque load ≥70% had a larger remodeling index (1.74 ± 0.52 *vs.* 1.19 ± 0.40, $P < 0.001$), more FF ($18.6 \pm 9.6\%$ *vs.* $8.5 \pm 8.6\%$, $P = 0.001$) and less DC ($5.6 \pm 4.1\%$ *vs.* $12.8 \pm 13.9\%$, $P = 0.037$) compared with lesions with plaque load <70%. However, it is a cross-sectional study, the temporary relationship between VH-IVUS findings and clinical characteristics cannot be determined. The latest research in China using VH-IVUS on high-risk plaque of SVGD found that: the FT was the main plaque component ($65.12 \pm 10.11\%$), FF 3.80% (5.40, 25.30), and the proportion of NC increased by 12.00% (5.40, 24.00), DC occupies only 1.00% (0.20, 3.80); plaques with ≥70% plaque burden are associated with more FF tissue. Graft age was positively correlated with FF tissue area ($r = 0.3$, $P = 0.047$), SVG lesion plaque area positive correlation with FF ($r = 0.64$, $P < 0.001$), positive correlation with NC ($r = 0.43$, $P = 0.003$); and the plaque burden was positively correlated with FF tissue area ($r = 0.50$, $P = 0.0004$) and positively correlated with the NC area ($r = 0.33$, $P = 0.028$).[48]

Application of VH-IVUS in the Interventional Therapy of SVGD

Non-reflow/slow blood flow during PCI of SVG is usually unpredictable, largely because of plaque ruptures and micro-thrombosis of distal blood vessels. The fundamental reasons for this are that plaque burden in SVG is underestimated prior to surgery, and the related prevention and treatment measures of distal thrombosis in PCI are inadequate. Many earlier studies demonstrated that the fat-rich NC identified by VH-IVUS is associated with no-reflow at the distal end after stent implantation.[25,26] Hong *et al*[20] confirmed, for the first time, that the positive remodeling of SVG observed by gray-scale IVUS was a solid predictor of no-reflow. Intraluminal plaques (OR: 4.84, 95% CI: 1.98–10.49, $P \leq 0.001$), multi-plaque rupture (OR: 3.46, 95% CI: 1.46–8.41, $P \geq 0.014$) and SVG (OR: 3.17, 95% CI: 1.17–6.56, $P \leq 0.024$) were all independent predictors of no-reflow after PCI. Gray-scale

IVUS, does, however, have limitations in distinguishing between fibrous plaques and fibrous fatty plaques. This technique is less sensitive (24%) for identifying small pieces of fatty plaque and is likely to ignore them.[49,50]

Previous studies have demonstrated that thin-cap fibroatheroma (TCFA), plaque burden, and MLA are associated with MACEs among ACS patients undergoing PCI.[21,22] The VIVA (VH-IVUS in Vulnerable Atherosclerosis) study showed that VH-IVUS TCFA was associated with non-restenotic and total MACEs on individual plaque or whole patient analysis.[22] It was reported by the PROSPECT (providing regional observations to study predictors of events in the coronary tree) study that plaque burden >70%, MLA < 4 mm^2, and VH-IVUS TCFA were the independent predictors of nonculprit lesion–related events.[51] Kang *et al*[52] found that an elevated plaque structural stress (PSS) was more likely associated with and the presence of VH-TCFA at 12-month follow-up and the VH-derived PSS was increased in plaques responsible for MACE. Kang *et al*[53] showed that nonculprit lesions in ST-segment elevation myocardial infarction (STEMI) patients were more unstable at the baseline compared with those in chronic total occlusion (CTO) patients, the diagnosis of STEMI and a large NC volume were predictors of evolution to a TCFA. Several studies had investigated the impact of plaque components on no-reflow after PCI in patients with ACS. A report by Hong *et al* in 2011[54] had found that post-PCI no-reflow was associated with larger NC area and more TCFAs in ACS patients. Besides, several meta-analysis studies found that absolute volume of NC component on VH-IVUS imaging was closely related to the distal embolization after PCI in ACS patients.[55,56] These studies suggested that identification of lesions with large amounts of NC on VH-IVUS be used to predict the undesirable side effect of PCI.

However, a limited number of studies have systematically investigated the possible angiographic prognosis predictors after SVG-PCI, data on plaque composition of SVG and its predictive values for clinical outcomes remained unclear. As far as the authors know, there is currently no study exploring the relationship between VH-IVUS defined atherosclerotic plaque components and clinical outcomes in SVGD patients undergoing PCI. Based on the similarity of pathophysiological mechanisms between CAD and SVGD, we thought that plaque characteristics of SVG assessed by VH-IVUS may be associated with clinical outcomes. Therefore, further studies with the larger sample size, the long-term follow-up, multicenter clinical trials may be warranted to validate the predictive value of our thoughts.

Interventional therapy of SVGD is still a major focus and challenge in the field of interventional cardiology. The emergence of VH-IVUS, iMap™ IVUS, etc. can conduct more in-depth study on the composition of SVGD plaques (especially vulnerable plaques), the plaque outcome, the relationship between plaque characteristics and cardiovascular adverse events. At the same time, with the rapid development of various imaging techniques in the intracoronary interventional field, it is possible to use the same catheter for different imaging examinations. VH-IVUS can be combined with other imaging and functional examination methods to provide a more complete field. Internal imaging and functional information drive the popularity and in-depth development of intravascular imaging technology.

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Conflicts of interest

None.

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