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Shedding Light Into Late Saphenous Vein Graft Failure

Tobias Koppara [a,c], Michael Joner [b,c]

[a] Klinikum rechts der Isar der Technischen Universität München, Munich, Germany
[b] Deutsches Herzzentrum München, Munich, Germany
[c] Deutsches Zentrum für Herz- und Kreislaufforschung e.V., Berlin, Germany

Coronary artery bypass graft (CABG) surgery remains a viable treatment option for patients with three-vessel coronary artery disease (CAD) or left main stenosis, as supported by many studies showing a long-term reduction in morbidity and mortality relative to percutaneous coronary intervention (PCI) [1–4]. Internal mammary arteries (IMAs) have proven to have the best long-term patency [5,6]. However, surgery entails implantation of single or bilateral internal mammary artery grafts in only 5–10% of cases because of increased perioperative mortality, duration of operation, and problems with sternal wound healing that are often reported for these types of grafts [7,8]. Although arterial grafts have proven superior for CABG, they are not always available because of the aforementioned limitations, which has led to the use of more easily harvestable saphenous vein grafts (SVGs) [9].

SVGs, unlike their arterial counterparts, are susceptible to the rapid development of atherosclerosis. Of note, 10–25% of SVGs occlude from thrombosis within 1 year after CABG [10,11]. Moreover, 4–5% occlude each year 6–10 years postoperatively, owing to accelerated development of atherosclerosis [12]. Hence, increasing failure rates result in need for percutaneous interventional vein graft procedures after 5 to 15 years [13].

1. Insights into late SVG atherosclerotic changes using optical coherence tomography

The article by Hsun-Wei Huang et al. [14] (*add REF*) compares morphological findings among native coronary arteries and SVGs from intravascular optical coherence tomography (OCT) imaging in 30 patients (15 SVGs and 15 native coronary arteries) presenting with non-ST segment elevation myocardial infarction (NSTEMI). The authors further provide intravascular imaging insights into potential failure modes of SVGs relative to native coronary arteries resulting in acute coronary syndrome (ACS) after a mean duration of approximately 14 years. Morphologic analysis showed increased presence of lesional lipid pools (lipid pool quadrants, 2.1 vs. 2.7; p=0.021), reduced fibro-atheroma cap-thickness in the SVG group (45.0 μm vs. 38.5 μm; p=0.05) and increased calcification (calcified lesion length = 0.4 mm vs. 1.8 mm; p=0.007; calcified quadrants = 0.2 vs. 0.9; p=0.001; arc of superficial calcium deposits = 11.6° vs. 50.9°; p=0.007) in the SVG group when compared to native coronary artery lesions. While the clinical and angiographic characteristics of SVG failure have been previously reported [15], the current study aimed at connecting clinical presentation with NSTEMI with intravascular imaging findings in degenerated vein grafts in a small-single center cohort and confirmed prior autopsy studies describing accelerated atherosclerotic change in vein grafts relative to native CAD [16]. Unfortunately, the authors neither discuss how those SVG lesions were treated nor share the clinical outcomes of those patients presenting with NSTEMI and SVG disease as compared to native CAD. Although the authors confirm the need for designated interventional strategies for late SVG failure, their report does not provide imaging insights of treated lesions following PCI, which leaves us with uncertainty of how those lesion characteristics impact on PCI results.

2. Are there characteristic hallmarks of SVG atherosclerosis?

Obstructive atherosclerotic lesions in native coronary arteries develop over decades, whereas accelerated atherosclerosis has previously been reported in SVGs within months to years in seminal autopsy studies [16,17]. Early changes can be observed within the first 72 hours after grafting, exhibiting a thin layer of platelets and fibrin deposited along the intimal surface of the vein graft [16]. Diffuse intimal hyperplasia consisting of smooth muscle cells in a proteoglycan and collagen-rich matrix is regularly observed in vein grafts after 1 month [18]. This remodeling process is believed to involve pathologic responses to endothelial injury and hemodynamic stress as the vein wall is subject to increased distending pressure of the arterial circulation.

In SVGs, further accelerated atherosclerosis likely develops from transmigrating and resident macrophage-derived foam cells, which undergo apoptosis and form necrotic core, while isolated lipid pool known from native atherosclerosis is rarely observed [16]. SVG stenosis is associated with the development and expansion of necrotic core and the occurrence of hemorrhage, leading to expansion and, eventually, rupture of the plaque. A better understanding of the mechanisms leading to SVG failure may facilitate the identification of patients at risk and enable development of robust therapeutic strategies. Along these lines, shedding light into SVG plaque morphology in patients with ACS as reported by Hsun-Wei Huang et al. using OCT provides the opportunity to identify *in vivo* characteristics of late graft failure and foster understanding of PCI outcomes in these patients.

What is known from previous post-mortem studies is the fact that SVGs undergo rapid transformation toward circumferential intimal thickening early after grafting, transitioning into formation of excessive necrotic cores with or without intraplaque hemorrhage arising from abundant neovascularization over 5-10 years [19]. Luminal stenosis remains low (34±15%) during the early phase of intimal thickening, likely

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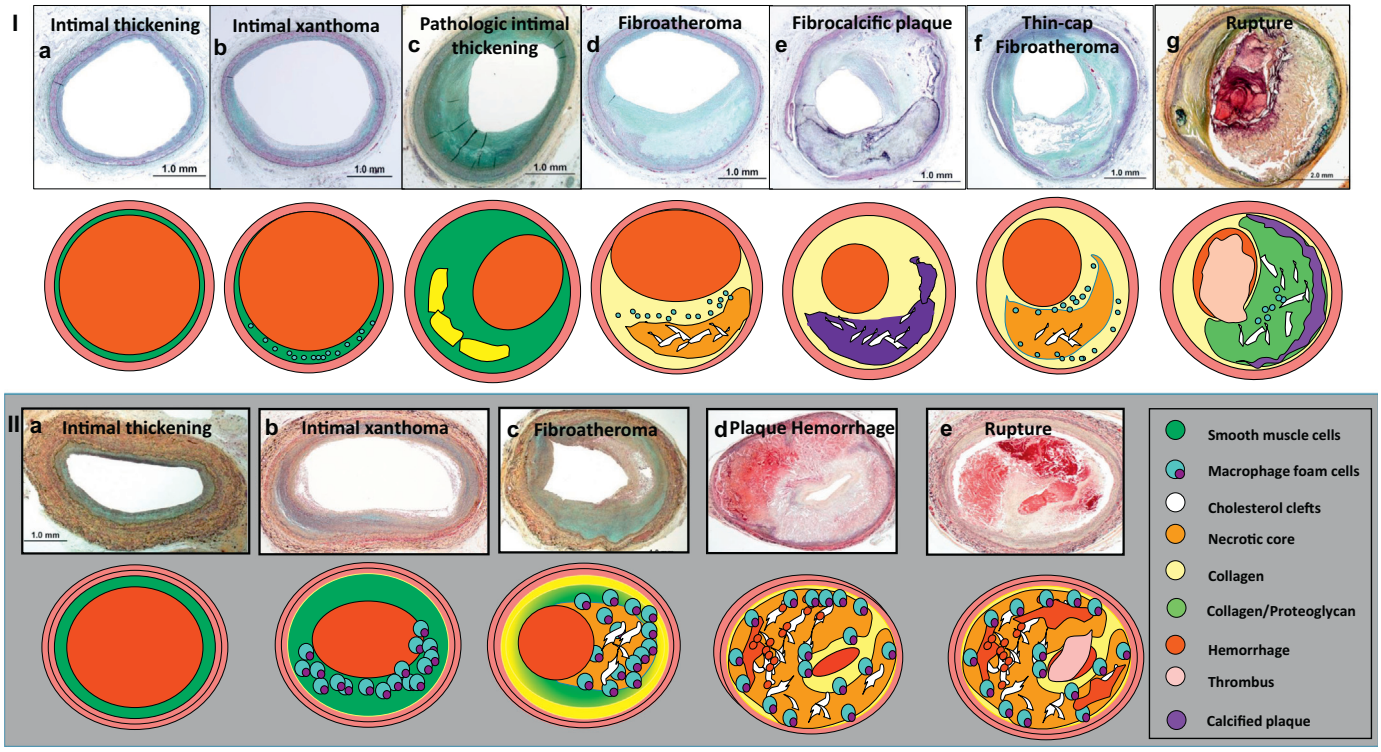

Fig. 1. Atherosclerotic disease in saphenous vein grafts and native coronary arteries. I. a) Intimal thickening. b) Intimal xanthoma. c) Pathologic intimal thickening. d) Fibroatheroma with necrotic core. e) Fibrocalcific plaque with calcified sheet. f) Thin-cap fibroatheroma with large necrotic core and thin fibrous cap. g) Plaque rupture with acute coronary thrombosis. II. a) Arterialization and intimal thickening of vein graft (within the first year). b) Progressive foam cell lesion. c) Formation of a necrotic core (within the 1st and 3rd years). d) Hemorrhage into the lipid core with moderate to severe luminal narrowing (after 4 to 5 years). e) Plaque rupture of a large necrotic core accompanied by hemorrhage and luminal thrombus (within 5 to 15 years). Reproduced and modified with permission from Yahagi K et al. [19].

not resulting in downstream ischemia, while rapid incline in luminal stenosis (75±24%) occurs from intraplaque hemorrhage into large necrotic core, eventually resulting in rupture of thin-capped fibroatheroma [19] (Fig. 1).

What has not been reported previously is the relative presence of advanced calcification in SVG lesions contributing to clinical manifestation with NSTEMI. Advanced stages of calcification are known from native coronary arteries [20] and have been linked to the clinical presentation of myocardial infarction [21], while soft atherosclerotic plaque rich in lipid and necrotic core has been predominant in SVG lesions to date [16]. Obvious consequences for PCI procedures may arise, ranging from protection against downstream embolization in soft SVG lesions to high-pressure non-compliant balloons with or without lesion debulking procedures in the presence of severe calcification. In keeping with this, intravascular imaging of SVG lesions may hold great potential to triage patients towards goal-oriented PCI procedures.

3. Do we have the right PCI strategies for late SVG disease?

The rapid acceleration in the development of atherosclerosis may enhance our understanding of poorer outcomes of SVG-PCI compared to PCI in native coronary anatomy [22]. Recent large-scale multicenter randomized controlled trials of drug-eluting stents (DES) versus bare-metal stents (BMS) in SVG showed no long-term differences between those two stent types after 1 to 5 years [23,24]. The reasons are still poorly understood but might be related to the chronic pathophysiologic changes leading to accelerated atherosclerosis and complex SVG plaque types. Whereas DES have shown superiority over BMS in SVG lesions with comparable graft age as reported by Hsun-Wei Huang et al. in 610 patients in a randomized study up to 1 year [25] long-term follow-up failed to show a benefit of DES use over BMS, which also implies differential late vascular healing responses in SVG as compared to native CAD. It has been noted in post-mortem specimens that implantation of stent struts into a large necrotic core causes extended delay in vascular healing, which might be augmented in DES relative to BMS owing to the release of anti-proliferative drugs [26]. Consequently, intravascular imaging of symptomatic SVG lesions may indeed hold potential to guide percutaneous procedures by identifying target lesions amenable to differential interventional strategies. It is without doubt that additional studies of prospective design are warranted before these suggestions become clinically adoptable.

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