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In vivo morphologic comparison of saphenous vein grafts and native coronary arteries following non-ST elevation myocardial infarction

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ABSTRACT

Objective: This study aimed to assess the pathophysiological differences between saphenous vein grafts (SVG) and native coronary arteries (NCA) following presentation with non-ST elevated myocardial infarction (NSTEMI).
Background: There is accelerated pathogenesis of de novo coronary disease in harvested SVG following coronary artery bypass (CABG) surgery, which contributes to both early and late graft failure, and is also causal in adverse outcomes following vein graft PCI. However *in vivo* assessment, with OCT imaging, comparing the differences between vein grafts and NCAs has not previously been performed.
Methods: We performed a retrospective, observational, analysis in patients who underwent PCI with adjunctive OCT imaging following presentation with NSTEMI, where the infarct-related artery (IRA) was either in an SVG or NCA.
Results: A total of 1550 OCT segments was analysed from thirty patients with a mean age of 66.3 (±9.0) years were included. The mean graft age of 13.9 (±5.6) years in the SVG group. OCT imaging showed that the SVG group had evidence of increased lipid pool burden (lipid pool quadrants, 2.1 vs 2.7; $p = 0.021$), with a reduced fibro-atheroma cap-thickness in the SVG group (45.0 μm vs 38.5 μm; $p = 0.05$) and increased burden of 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°; $p = 0.007$) when compared to NCA.
Conclusion: This OCT study has demonstrated that vein grafts have a uniquely atherogenic environment which leads to the development of calcified, lipogenic, thin-capped fibro-atheroma's, which may be pivotal in the increased, acute and chronic graft failure rate, and may underpin the increased adverse outcomes following vein graft PCI.

1. Introduction

Percutaneous coronary intervention (PCI) is the commonest mode of coronary revascularization therapy, however, coronary artery bypass graft (CAGB) surgery remains an important treatment modality, particularly in multi-vessel and left main disease. The internal mammary artery is the conduit of choice due to its superior long-term patency [1,2]. However many patients require additional grafts to provide complete revascularization, most commonly with the use of saphenous veins (SVG) [3]. These conduits are known to have higher rates of early and late graft failure compared to arterial conduits, with the underlying pathogenesis in this process postulated to be linked to the adverse outcomes seen in the context of vein graft PCI [4].

Optical Coherence Tomography (OCT) provides high resolution intra-coronary imaging, enabling intravascular morphology and pathological characterisation to be delineated. High spatial resolution afforded by OCT imaging, approaching that of a histopathological sample [5], allows an in-vivo '*optical biopsy*' to be performed. It is, therefore, uniquely placed to provide insights into the pathogenesis of coronary disease, and specifically in the context of vein graft disease progression [6,7].

Whilst there are postulations about the pathophysiological processes underpinning the increased rate of disease progression in vein grafts, there are limited OCT data characterising the morphological features of vein graft failure, specifically in the context of acute coronary syndromes (ACS) [8]. The purpose of this study was to use OCT imaging to compare the *in vivo* morphologic characteristics of lesions within SVGs and native

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coronary arteries (NCAs) respectively, in a cohort presenting with non-ST elevation myocardial infarction (NSTEMI).

2. Methods

2.1. Patient population data

This was a retrospective analysis of consecutive patients admitted with an NSTEMI, in whom PCI with adjunctive OCT imaging was performed in the angiographically determined IRA, between September 2014 and January 2016. The study definition of an NSTEMI was a patient presenting with chest pain with associated ECG changes (T-wave inversion and/or ST depression) with an elevated troponin assay. All baseline data was collated which included patient demographics and risk factors profile (Table 1). Ethical approval for the study was provided by institutional ethics committee.

2.2. OCT protocol

All OCT imaging were performed using the C7 Dragonfly™ with a pullback speed of 20 mm/s and the ILUMIEN™ PCI Optimization System (St. Jude Medical) in the angiographically determined target vessel. A column of contrast medium (iso-osmolar iodixonoal, Visipaque™ by GE healthcare) was injected into the coronary artery via an automated pump or manual injection. During the administration of contrast medium OCT imaging was performed with a pullback speed of 20 mm/s and acquisition of 100 frames/s. OCT imaging was performed before any intervention was performed after guide-wire placement into the distal vessel. Image data were stored digitally for subsequent post-hoc analysis.

2.3. OCT analysis

OCT imaging calculations were performed using the proprietary software (St Jude Medical, U.S.A) at 0.4 mm intervals. Two investigators independently analyzed the data, blinded to the clinical history and the nature of the vessel (SVG or native artery) being analysed. In the event of a difference in opinion then a third investigator would adjudicate to allow a consensus to be formed. The OCT data were analyzed based upon the plaque characteristic classification previously described, with a minimum of three quadrants of the lumen required to be considered sufficient for analysis [9,10]. Briefly, proximal and distal reference vessel areas (mm^2) and diameters (mm) were measured at the largest lumen site within 5 mm outside the lesion's edges. The mean value of proximal and distal measurements was used. Minimal lumen area (MLA) and minimal flow area were determined. Culprit lesion morphology of all cases was analysed by two independent observers (THW and KDS). Plaque rupture was defined as fibrous cap discontinuity usually associated with cavity formation [12]. Intact fibrous cap included both definite and probable erosions, the former defined as thrombus overlying a visualised intact cap and the latter as thrombus or luminal irregularity without a visible rupture site [12,13].

Nodular protruding calcium or a heavily calcified plaque usually with associated thrombus was defined as a calcified nodule. In addition, type of thrombus and location of rupture were assessed. For plaque composition analyses, the culprit lesion was defined by the number of consecutive frames containing ≥2 diseased quadrants. Plaque composition was analysed at 1 mm intervals over the length of the lesion using standard definitions [9]. At each interval, the number of quadrants with different plaque types (fibrotic, calcified, or lipid) was recorded. The plaque types were defined as follows: fibrous tissue was defined as signals that show high back-scattering (Fig. 1a); lipid containing plaque were defined as signals with lower density and greater heterogeneous back-scattering than fibrous plaques; calcified plaques were defined as a lesion with a well-delineated heterogenous region with reduced back-scatter (Fig. 1b) [9]. These counts were summed over the length of the lesion to determine the total number of quadrants for each plaque type per lesion. The length of lipid pool was measured as consecutive longitudinal length of lipid pool at culprit plaque as previously described [11]. Minimal fibrous cap thickness (FCT) was recorded as a mean of three measurements at the lesion site where the thinnest cap was observed. A FCT of ≤65 μm, was used to define the lesion as a thin-cap fibroatheroma (TCFA) (Fig. 1c and d). The arc (in degrees), the longitudinal extent of a superficial necrotic lipid pool characteristic was measured [13].

2.4. Statistical analysis

Statistical analysis for this study was based on the published methodology by Davlouros et al [14]. All data were summarised as group percentages where possible, with continuous data summarised as mean ± standard deviation (SD). A one-way Analysis of variance (ANOVA) test was performed comparing the two groups, SVG and NCA respectively. The relationship between demographic and OCT morphological characteristics were assessed using a univariate analysis. All variables found to be significant ($P < 0.05$) in the univariate model where then incorporated into a multivariate model. All tests were two-tailed and p-values of <0.05 were considered statistically significant. The statistical analysis was performed using SPSS for Windows (Version 22.0, SPSS, Chicago, U.S.A).

3. Results

Forty-eight patients presenting with an NSTEMI were recruited into the study. Eighteen patients were excluded because no culprit lesion was identified and PCI was not performed (n = 11), the presence of multi-vessel disease precluding further assessment (n = 4) and intra-procedural haemodynamic instability (n = 3). Thirty patients, with a mean age of 66.3 (±9.8), were included in the final analysis (n = 15 SVG and n = 15 NCA). Whilst there was an increased incidence of hypertension in the SVG group (n = 7 vs. n = 14; p = 0.004), there were no other significant differences in baseline characteristics (data are summarised in Table 1). All angiographically determined, culprit vessels had TIMI 3 flow, allowing pre-PCI OCT interrogation to be performed successfully in all cases. 1550 OCT segments were analysed from a total of 38 lesions across both groups. OCT examination revealed 18 probable or definite plaque rupture lesions (NCA n = 6 versus SVG n = 12, p = 0.044) and 20 probable or definite plaque erosion lesions (NCA n = 9 versus SVG n = 11, p = 0.211). The SVG cohort (n = 15), had a mean vein graft age of 13.9 (±5.6) years, with graft age of >15 years being associated with an ACS presentation (p = 0.001).

The OCT image analysis revealed no differences in minimal luminal area in the culprit vessels between the NCA group and SVG group (2.8 mm^2 (±1.2) vs. 2.6 mm^2 (±2.1), p = 0.65). The target vessel reference mean diameter was 3.47 mm (±0.40) compared to 3.52 mm (±0.61)

Table 1
Baseline demographic data and OCT characteristics.

	NCA (n = 15)	SVG (n = 15)	P-value
Patient demographics			
Age (years)	64.9 (±10)	69.7 (±8)	0.06
Hypercholesterolemia	13 (87%)	13 (87%)	1.000
Hypertension	7 (47%)	14 (93%)	0.004
Currently smoking	2 (13%)	6 (40%)	0.105
Diabetes mellitus	3 (20%)	7 (47%)	0.130
Medical therapy			
Statins	14 (93%)	12 (80%)	0.299
ACE inhibitors or ARB	8 (53%)	12 (80%)	0.130
Antiplatelet therapy	14 (93%)	10 (67%)	0.072
Beta-blockers	12 (80%)	11 (74%)	0.679
Calcium-channel antagonists	2 (13%)	5 (33%)	0.208

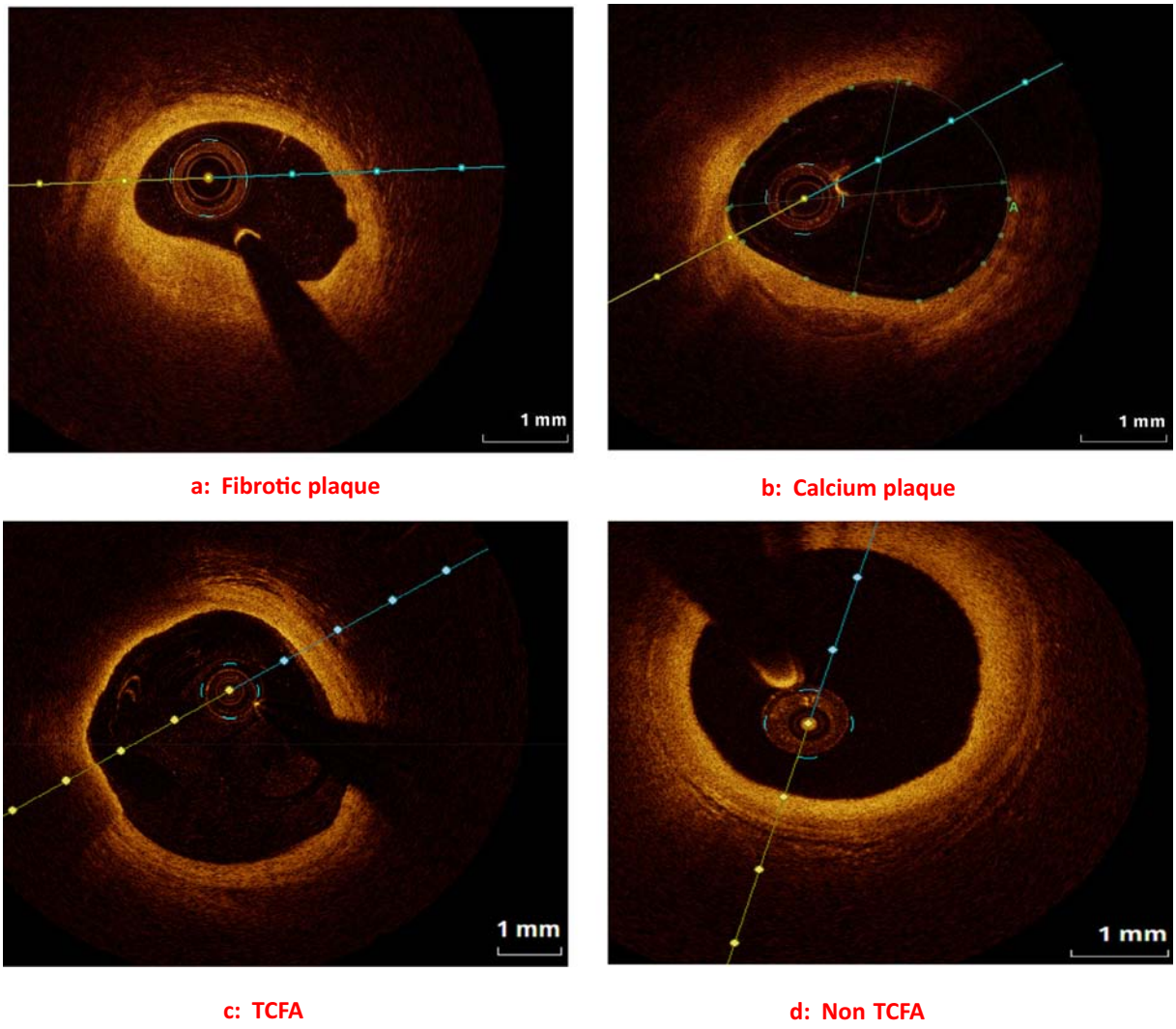

Fig. 1. a) Fibrotic plaque, b) calcified plaque, c) TCFA lesion, d) non-TCFA lesion.

($p = 0.810$) and a mean area of 8.99 mm^2 (± 2.37) versus 10.13 mm^2 (± 3.14) ($p = 0.325$) in the NCA and SVG groups respectively.

There was increased frequency of thin-cap fibro-atheroma (TCFA) in the SVG group ($n = 6$ (NCA) vs. $n = 13$ (SVG); $p = 0.01$) with the mean fibro-atheroma cap thickness being significantly less (45.0 μm vs 38.5 μm; $p = 0.05$). There was also increased lesion calcification in the SVG group, with a significant increase in calcified lesion length (0.4 mm vs 1.8 mm; $p = 0.007$), calcified quadrants (0.2 vs 0.9; $p = 0.001$), and arc of superficial calcium deposition (11.6° vs 50.9°, $p = 0.007$) (Fig. 2a–b, Table 2). The SVG group also had an increased lipid burden, evidenced by increased lipid pool quadrants (2.1 vs 2.7; $p = 0.021$) (Fig. 2c–d; Table 2), arcs (159.8° vs 209.3°; $p = 0.007$). Univariate analysis of plaque characteristics promoting ACS included calcification, lipid burden, and the presence of TCFA. Subsequent multi-variate analysis revealed that calcification and lipid pool remained independent factors associated with ACS presentation, both of which are predominant morphological features in the SVG-group (Table 3).

4. Discussion

Optical coherence tomography is an insightful intravascular technique that allows accurate characterisation of coronary disease, and has been widely adopted in interventional cardiology over the past decade [16–20]. This is the first *in vivo* study utilizing OCT to compare the morphological differences between native coronary artery disease and saphenous vein grafts in patients presenting with acute coronary syndrome. This study has demonstrated that, in an age-matched cohort, vein grafts have the propensity to develop an increased burden of lipid rich plaque, with more friable thin-capped fibro-atheromas, and increased lesion calcification. These underlying plaque characteristics are likely to be pivotal in acute and chronic graft failure, and may also underpin the adverse outcomes associated with PCI in vein grafts.

The pathophysiology of acute coronary syndrome is caused by the abrupt, complete, or incomplete occlusion of a coronary vessel due to plaque rupture or erosion, with subsequent thrombus formation and possible intermittent vasospasm [15]. Histopathological assessment of vein grafts has suggested an increased burden of plaque with more friable, TCFA lesions, leading to an increased chance of rupture and thrombus formation [8]. The majority of patients undergoing CABG, continue to have vein grafts used in addition to arterial grafts. This relates to its ready availability of these conduits, and technical surgical considerations, with veins being easier to harvest and establish anastomoses, whilst also minimising the risk of sternal wound infection, compared to arterial conduits [21]. The current study reaffirms previous histological investigation about the potential intrinsic pathophysiological changes that occur vein grafts, with the development of a more

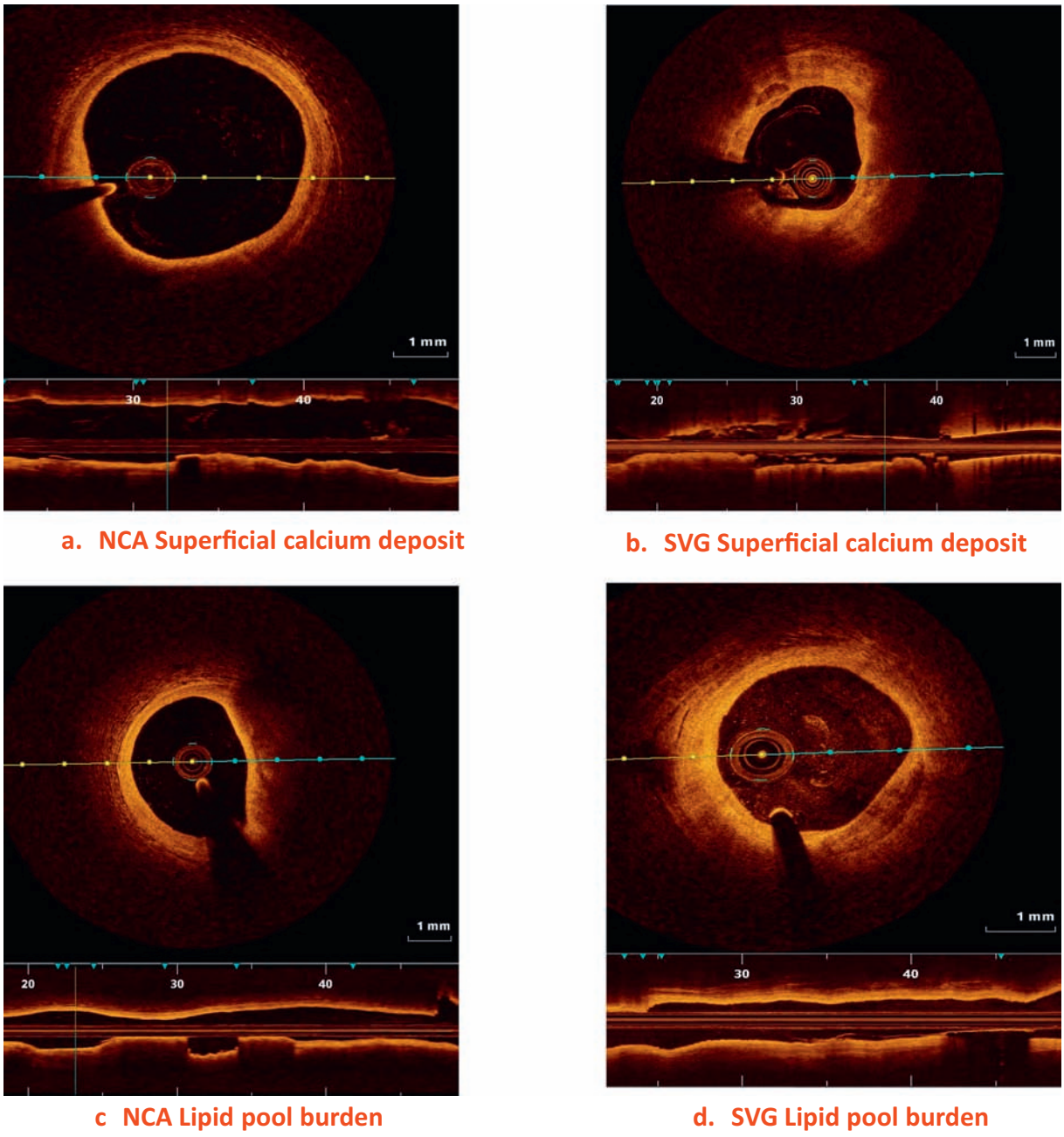

Fig. 2. OCT determined differences in lesion calcification by a) lesion length and b) quadrant analysis.

atherogenic environment, that is comprised of disease that is more prone to acute plaque rupture, and therefore, acute vessel closure, which may also adversely impact long-term graft patency.

Following surgical harvesting and anastomosis, vein grafts adapt to their new arterial environment by processes such as intimal hyperplasia, geometric re-modelling, wall stiffening, and inflammation [22]. A degree of intimal hyperplasia formation is necessary to allow appropriate arterialization and long-term graft patency. However, why some grafts stop re-modelling after arterialization while others progress to develop stenoses remains unclear. Patency rates of vein grafts diminish from 98% immediately after surgery to <88% within the first month post-surgery owing to acute thrombosis, reducing further to 40–75% patency at 10-years [23]. The mechanisms that underpin this attrition rate may relate to the intra-and post-operative period where immediately after harvesting, venous conduits undergo a period of ischemia and reperfusion after engraftment, resulting in endothelial cell and smooth muscle cell damage [22,24]. Additionally, uncontrolled smooth cell proliferation and extensive extra-cellular matrix deposition contribute to excessive intimal hyperplasia accelerating the process of vein graft failure by forming an unstable atherosclerotic environment [25,26].

4.1. Pathogenesis of coronary disease in saphenous vein grafts – mechanistic insights

Previous studies have shown that SVG plaque morphology has increased fragility and more prone to ulceration compared to the native circulation [27]. Unni et al described that within one month to a year after bypass surgery, the predominant pathology identified in failed grafts was neointimal hyperplasia [28]. A further observational study showed that the degeneration of vein grafts may not be linearly related to age, with the suggestion that there is a more rapid acceleration in the

Table 2
Univariate analysis of OCT determined characteristics of culprit lesions; native vessels vs. vein grafts.

	NCA	SVG	
	(n = 15)	(n = 15)	P-value
Anatomic data			
LAD (%)	8	3	n/a
LCx (%)	3	8	n/a
RCA (%)	4	4	n/a
Graft age (years)	n/a	13.9 (±5.4)	n/a
TCFA-cap thickness (μm)	45.0 (±4.8)	38.5 (±11.2)	0.047
Presence of thrombus	6 (40%)	11 (73%)	0.069
Minimum luminal area (mm^2)	2.8 (±1.2)	2.6 (±2.1)	0.651
Maximum luminal area (mm^2)	9.8 (±3.5)	12.2 (±7.6)	0.281
Minimum lumen diameter (mm)	1.8 (±0.4)	1.7 (±0.6)	0.824
Maximum lumen diameter (mm)	3.4 (±0.5)	4.1 (±1.6)	0.123
Vessel length (mm)	43.2 (±5.2)	43.7 (±11.9)	0.899
Calcium burden by quadrants			
Calcified lesion length (mm)	0.4 (±1.1)	1.8 (±1.5)	0.007
Calcium quadrants/frame-	0.2 (±0.6)	0.9 (±0.5)	0.001
Arc of superficial calcium deposits (degree)	11.6 (±33.1)	50.9 (±41.5)	0.007
0–90° (%)	1 (7%)	11 (73%)	0.001
90–180° (%)	1 (7%)	1 (7%)	1.000
180–270° (%)	0.0	0.0	n/a
270–360° (%)	0.0	0.0	n/a
Lipid burden			
Lipid pool length (mm)	15.9 (±7.9)	17.9 (±11.7)	0.589
Lipid pool–quadrants/frame-	2.1 (±0.6)	2.7 (±0.7)	0.021
Lipid pool Arc (degree)	159.8 (±43.9)	209.3 (±62.9)	0.007
0–90° (%)	2 (13%)	0.0	0.019
90–180° (%)	9 (60%)	5 (33%)	0.153
180–270° (%)	4 (27%)	4 (27%)	1.000
270–360° (%)	0.0	2 (13%)	n/a
Lesion classification			
Probable/definite plaque rupture	6	12	0.044
Probable/definite plaque erosion	9	11	0.211

development of atherosclerosis after ten years compared to prior to this period [29]. This is likely due to the constant exposure of SVG to high systemic arterial pressure flow resulting in endothelial intimal damage proceeding to a mature atherosclerotic plaque formation [26,30,31]. In keeping with these previous findings, the current study has reasserted this notion, that grafts, of greater than fifteen years of age, were more likely to associated with ACS, reaffirming the accelerated degeneration of vein grafts with increasing age.

4.2. Percutaneous revascularization in vein grafts

Despite the increasing regularity in which it is performed, and the use of the latest drug-eluting stent devices and anti-platelet therapy, SVG-PCI continues to be associated with poorer outcomes compared to PCI in native coronary anatomy [32]. Our data has reiterated that vein grafts represent a particularly high-risk substrate for PCI. The presence of specific morphological features, such as increased lipogenecity, along with an increased frequency of 'high-risk' TCFA lesions, suggest that PCI, in the context of this unique microenvironment, may be prone to long-term failure; due to the combination of an accelerated intimal response, and the heightened athero-thrombotic risk posed by these vessels.

Table 3
Multivariate analysis of OCT determined characteristics of culprit lesions; native vessels vs. vein grafts.

	NCA	SVG	
	(n = 15)	(n = 15)	P-value
TCFA-cap thickness (μm)	45.0 (±4.8)	38.5 (±11.2)	0.080
Calcified lesion length (mm)	0.4 (±1.1)	1.8 (±1.5)	0.031
Calcium quadrants	0.2 (±0.6)	0.9 (±0.5)	0.047
Arc of superficial calcium deposits (degree)	11.6 (±33.1)	50.9 (±41.5)	0.042
Lipid pool–quadrants/frame-	2.1 (±0.6)	2.7 (±0.7)	0.068
Lipid pool arc (degree)	159.8 (±43.9)	209.3 (±62.9)	0.038

There is an increased understanding that vein graft PCI has limited long term durability and that treatment of the native vessel is likely to provide a more durable long-term result [33]. The complexity of coronary disease being treated percutaneously has evolved over the last two decades. Chronic total occlusion (CTO) PCI techniques, utilizing both antegrade and retrograde techniques, to recanalise native anatomy is the primary goal in this expanding niche within PCI therapy. Techniques have developed to incorporate the use of vein grafts as conduits to access occluded native vessels, with subsequent retrograde recanalization performed with increasing frequency and success [34]. However future directions will be based upon clinically directive data in the CTO field, which are still awaited [33].

4.3. Study limitations

There are several limitations to this study. Firstly, this is a single centre study with a small sample size, meaning that subsequent inferences are limited due to type 1 error. Secondly, the data collected were via a retrospective, non-randomized fashion, and whilst the two groups were well matched, the morphological differences seen on OCT examination may not be representative of the wider population. The identification of the culprit vessel was by angiographic appearance, rather than systematic OCT examination. As it is well established that plaque rupture and/or erosion can co-exist in a number of vessels during a single ACS presentation, the true 'culprit' may not have been interrogated and therefore the results may not be truly representative. Nonetheless, the determination of the culprit artery was performed in a manner in keeping with 'real-world' practice and therefore remain applicable. Finally, further studies assessing vein graft pathophysiology should be large, and multi-centred, to try and further identify the innate mechanisms that render this form of bypass conduit high-risk of failure, both following surgery and after PCI procedures.

5. Conclusion

This OCT study has demonstrated that vein grafts have a uniquely atherogenic environment which leads to the development of calcified, lipogenic, thin-capped fibro-atheroma's, which may be pivotal in the increased, acute and chronic graft failure rate, and may underpin the increased adverse outcomes following vein graft PCI.

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We have no acknowledgement to declare.

Conflicts of interest

We have no conflicts of interest to declare.

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