OCT imaging of aorto-coronary vein graft pathology modified by external stenting: 1-year post-surgery

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Aims

The Venous External Support Trial (VEST) evaluated whether a novel external stent attenuated saphenous vein graft (SVG) disease assessed with intravascular ultrasound 1 year following coronary artery bypass graft (CABG) surgery. This sub-study assessed SVGs with and without external stenting using optical coherence tomography (OCT). The aim of this study was to accurately compare quantitative and qualitative features of SVGs with and without a novel external stent using OCT.

Methods and results

Twenty-four of 30 patients (65 ± 8 years) enrolled in VEST underwent coronary angiography with OCT imaging using a non-occlusive technique. Quantitative analysis of lumen area was performed in one frame every 10 mm along the length of the graft, from distal to proximal anastomosis, and pathological features within the lumen were noted. Mean cross-sectional area was greater in unstented vs. stented grafts (8.4 ± 3 vs. 7.6 ± 2.7 mm; \( P = 0.005 \)). The lumen of the stented grafts was more homogeneous (difference between maximum and minimum lumen diameter was significantly smaller in stented compared with unstented grafts, 0.28 ± 0.19 vs. 0.33 ± 0.23 mm, respectively, \( P = 0.006 \)), and more circular (mean eccentricity index 0.08 ± 0.06 vs. 0.10 ± 0.06, stented vs. unstented; \( P = 0.019 \)). Adherent thrombus was identified in three grafts (all unstented).

Conclusion

Our findings highlight the early changes occurring in SVGs after implantation of aorto-coronary bypass conduits, changes that may accelerate vein graft failure. External stenting resulted in a more homogeneous and less eccentric lumen with no thrombus formation.

Keywords

bypass • imaging • stents • surgery • veins

Introduction

Despite evidence supporting the superior long-term patency of arterial conduits in coronary artery bypass graft (CABG) surgery, saphenous vein grafts (SVGs) remain a widely used conduit. The Venous External Support Trial (VEST) examined whether a novel external stent would beneficially affect intimal hyperplasia after 1 year.1 Using intravascular ultrasound (IVUS), VEST showed that external stenting significantly reduced SVG intimal hyperplasia 1 year after CABG surgery.1 IVUS generally characterizes the entire depth of the vessel wall with a spatial resolution of 100–200 μm. Optical coherence tomography (OCT) on the other hand has greater spatial resolution and therefore gives superior image quality but with less depth of field. It is useful therefore in characterizing the luminal features of blood vessels and is a validated method for characterizing the vessel wall of SVGs.2 OCT imaging was performed at the time of 1 year following angiography, but because of the limited penetration, OCT was unable to offer data on the primary end point of the study and so OCT results were not reported in the primary publication.

In the present study, we examined SVGs with and without a novel external stent using OCT, with the aim of accurately comparing their quantitative and qualitative features.
Methods

Patients
VEST was a prospective, multicentre, randomized, self-controlled trial that has been described in detail previously (Clinical Trial Registration—http://www.clinicaltrials.gov, Unique identifier: NCT01415245). Briefly, patients aged 50–80 years were eligible if they were scheduled for on-pump multi-vessel CABG including a left internal mammary artery to the left anterior descending coronary artery and SVGs to right and circumflex territories. Each patient received one external stent device to a single SVG, randomly assigned intra-operatively, to either the right or the circumflex coronary territory. One or more SVGs remained unstented and served as the control group. Patients underwent coronary angiography of all grafts, and IVUS and OCT imaging of SVGs to the right and circumflex territories 12 months post-operatively. All patients were routinely treated post-operatively with aspirin, beta-blockers and statins according to maximum tolerable dose (but not a specific target low-density lipoprotein cholesterol concentration). The study was approved by an institutional review committee, and the subjects gave written informed consent.

The stent
The expandable external support stent is made from braided cobalt—chromium—nickel—molybdenum—iron fibres [Vascular Graft Solutions (VGS) Ltd, Tel Aviv, Israel]. The aim of the device is to prevent graft kinking and dilatation, reduce wall tension, and maintain uniform cross-sectional area (CSA) and wall thickness (i.e. prevent or reduce intimal hyperplasia), factors known to affect graft failure. It has been tested successfully in sheep, and VEST was the first in man study.

Optical coherence tomography
OCT images were acquired using the Ilumien system (St. Jude Medical, Minneapolis, MN, USA) using a non-occlusive technique following a 200 µg intracoronary nitrate bolus. This technique entails an infusion of non-ionic contrast solution through the guide catheter by an automated injection at a rate of 1–3 mL/s. During imaging, the OCT catheter was pulled back at a speed of 20 mm/s, and images were acquired at a rate of 100 frames/s with a maximal length of the imaged segment of ~5 cm. Detailed descriptions of OCT methodology and application have been published previously. The entire length of the randomized and control grafts, from the distal anastomosis to the proximal anastomosis, was imaged in a series of up to three pullbacks per graft.

Images were stored on digital video disc and analysed offline using specialist software [either Ilumien Analysis Package (St. Jude Medical) or QIVUS® 2.2 (Medis, Leiden, The Netherlands)] by an independent observer. Automated measurements of lumen CSA and mean, minimum, and maximum diameters were made approximately every 10 mm along the graft from the distal to the proximal anastomosis. Lumen eccentricity was calculated as previously described [(max−min)/max diameter]. Morphological features throughout the graft such as thrombus and calcium were characterized.

Data analysis
Student’s t-test was used for continuous variables. Significance was set at 5%, and data are presented as mean ± standard deviation. Results were analysed using Excel 2010 (Microsoft Corporation, USA).

Results

Patients
Twenty-four of the 30 patients enrolled in VEST underwent OCT imaging and are characterized in Table 1. One unstented graft and 4 stented grafts were occluded at the time of imaging; therefore, OCT data were available in 43 grafts (23 unstented and 20 stented). Conduit length at surgery was not different between stented and unstented grafts (15 ± 2 vs. 15 ± 3 mm, respectively; \( P = 0.85 \)).

Quantitative comparison
Mean lumen CSA was greater in unstented than stented grafts (mean 8.4 ± 3 vs. 7.6 ± 2.7 mm², respectively, \( P = 0.005 \); range 3.1–18.6 vs. 1.8–17.8 mm²); however, there was no difference in

Table 1 Patient characteristics (n = 24)

| Age (years) | 65 ± 8 |
| Male       | 22 (92) |
| Height (cm) | 173 ± 7 |
| Weight (cm) | 84 ± 9 |
| Smoking status |
| Current    | 2 (8) |
| Ex-smoker  | 19 (79) |
| Never      | 3 (13) |
| Diabetes   |
| IDDM       | 5 (21) |
| NIDDM      | 5 (21) |
| No history | 14 (58) |
| Hypertension | 16 (66) |
| Hyperlipidaemia | 22 (92) |
| Prior stroke (non-debilitating) | 1 (4) |
| NYHA class |
| I          | 9 (39) |
| II         | 11 (48) |
| III        | 3 (13) |
| Data not available | 1 (4) |

IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus. Data are expressed as mean ± SD or n (%).

Figure 1 Frequency of lumen eccentricity values. Lumen eccentricity of SVGs was significantly smaller in stented (black bars) than in unstented (white bars) grafts. Overall \( P = 0.019 \).
maximum–minimum CSA difference in stented and unstented grafts (4.96 ± 2.98 vs. 4.66 ± 2.45 mm², \(P = 0.72\)). Minimum lumen diameter was similar in stented and unstented grafts (3 ± 0.57 and 3 ± 0.54 mm, respectively, \(P = 0.88\)); however, maximum lumen diameter was greater in unstented grafts (3.22 ± 0.59 vs. 3.40 ± 0.62 mm, stented vs. unstented, \(P = 0.002\)). The difference between maximum and minimum lumen diameters was significantly smaller in stented compared with unstented grafts (0.28 ± 0.19 vs. 0.33 ± 0.23 mm, respectively, \(P = 0.006\)), and lumen eccentricity was significantly smaller in stented than in unstented grafts (mean values 0.08 ± 0.06 vs. 0.10 ± 0.06, respectively, \(P = 0.019\); Figure 1).

### Qualitative comparison

Figure 2 shows OCT images and associated angiograms from SVGs with and without a VEST in situ. Organized adherent thrombus was seen in three grafts, which were all unstented (13% of unstented grafts; Figure 3). No calcium deposits were seen. Other notable features are shown in Figure 4.

**Figure 2** Vein grafts with and without an external stent. Angiograms of SVGs with (A) and without (C) an external stent in situ. The white arrow in each angiogram depicts the position of the OCT image (B and D, respectively). The external stent struts appear as regular bright white lines on OCT (white arrow in B).
Discussion

This study demonstrates that OCT is useful for characterizing luminal features of SVGs not clearly seen using IVUS, similar to a previous study in SVGs, and is helpful to identify differences in SVGs with and without external stent support. Measurement of lumen geometry revealed a smaller lumen area and reduced lumen eccentricity in supported grafts. This indicates that supported grafts have a more uniform lumen than unsupported grafts, and quantitatively confirms the angiographic qualitative findings assessed using the Fitzgibbon classification that was reported in the main VEST publication. This is important as lumen irregularities are progressive in SVGs and may prelude the development of significant atherosclerotic lesions.

Intraluminal features

Whilst IVUS imaging reported one thrombus in our study (also noted in OCT analysis), OCT showed two further thrombi, all in unstented grafts (13% of unstented grafts). Histological examination of aorto-coronary vein grafts in another study investigating this external stent reported a 30% incidence of organized thrombosis in SVGs at 3-month follow-up. Since thrombosis is the main mechanism of aorto-coronary graft occlusion within the first year, caused by a combination of intimal damage, changes in blood flow and hypercoagulability, this is a notable finding. The lack of thrombus in stented grafts may be at least partly explained by an indirect effect of the stent on thrombomodulin expression. Thrombomodulin is produced by the endothelial cells and is important in blood vessel thromboresistance, and recent evidence suggests that thrombomodulin expression in vein grafts is regulated by exposure to arterial pressure. The external stent has the potential to reduce vessel wall tension in aorto-coronary vein grafts, thereby reducing the potential to thrombosis at least in part by maintaining thrombomodulin protein expression. In addition to thrombus, OCT revealed other luminal features such as venous valves, dissections, and side-branch clips that all have the potential to affect graft patency via effects on lumen uniformity. Metal clips were used in one of the two centres that recruited patients into the study whilst the other used ties. Interestingly, lumen eccentricity was significantly greater in unstented grafts treated in the centre that used metal clips than in the centre that used ties (0.10 ± 0.06 vs. 0.08 ± 0.06, P = 0.04), while there was no difference between centres for stented grafts (P = 0.7).Whilst the numbers are small, therefore these data must be interpreted with caution, it is an interesting observation that may be worthy of confirmation in larger studies.

Luminal geometry

Our observations demonstrate that SVG lumens are not always circular or regular. The smaller lumen eccentricity index seen in stented grafts indicates a tendency for these vessels to be more circular, which in turn may have an influence on blood flow patterns within the conduit. The more uniform and circular lumen achieved with the use of an external support stent has implications for flow measurements or estimations that use mathematical or geometrical modelling, with its inherent assumptions of circularity and smoothness. Clinically, the VEST can improve luminal flow patterns and hemodynamic parameters in SVGs by reducing oscillatory shear stress. Laminar flow with sustained, physiological, laminar shear stress is known to maintain vascular homeostasis and combat thrombosis and atherosclerosis. Conversely, disturbed flow with low and changeable shear stress can negatively affect atherogenic and thrombogenic processes. Increased lumen eccentricity, as well as greater lumen size leading to greater incidence of intimal hyperplasia, may at least partly explain the decreased longevity of SVG vs. arterial grafts after CABG surgery.

Limitations

The main VEST results did not report the OCT results as many of the conduits were too large to image the entire circumferential depth of the vessel wall. This led to difficulties accurately depicting

Figure 3 Thrombus. Cross-sectional OCT images of two of the three thrombi characterized in unstented SVGs. The white arrows depict thrombus.
Figure 4 OCT images of other notable features. (A) Venous valve within a stented SVG. The arrow depicts the valve leaflets. (B) Dissection within a stented SVG. The arrow depicts the dissection. (C) Side branch with clip. The arrow depicts the clip. (D) Clips inside the VEST. The arrow depicts the clips. (E) Lumen irregularity.
the intima/external elastic lamina/adventitial borders of the conduits in many cases, and an inability to accurately measure the primary end point of intimal hyperplasia, or fully define pathological features of the vessel wall. Despite this, OCT provided more detailed intraluminal anatomic data and we feel that the OCT images of this first-in-man study are worth sharing with the medical and scientific communities.

We cannot comment on early patency data from the VEST study; however, there were no complications reported at the 6-week follow-up visit.\(^1\) Transit time flow measurements (TTFM) were used to ensure intraoperative graft patency; however, we acknowledge controversies in the literature regarding the limitations of this measurement and the ‘cut-off’ values that predict long-term patency with regard to overall flow, pulsatility index, degree of diastolic filling, and backflow.\(^ {13,14} \) Furthermore, TTFM will not predict graft failure due to poor vein graft quality or thrombosis due to hypercoagulability or suboptimal anti-thrombotic treatment.

### Conclusions

OCT characterized luminal features of SVGs not clearly seen using IVUS, and identified differences in SVGs with and without external stent support. Supported grafts have a more uniform lumen than unsupported grafts—this is an important finding as lumen irregularities are associated with suboptimal flow patterns that may result in endothelial dysfunction and the development of significant atherosclerotic disease.

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### Conflict of interest

E.O. is a co-inventor of VEST, CEO, and board member of Vascular Graft Solutions Ltd with stock ownership. D.P.T. is a consultant to Vascular Graft Solutions with stock options ownership.

### References