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ORIGINAL ARTICLE

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Vasa vasorum of the no-touch saphenous vein graft observed using frequency-domain optical coherence tomography

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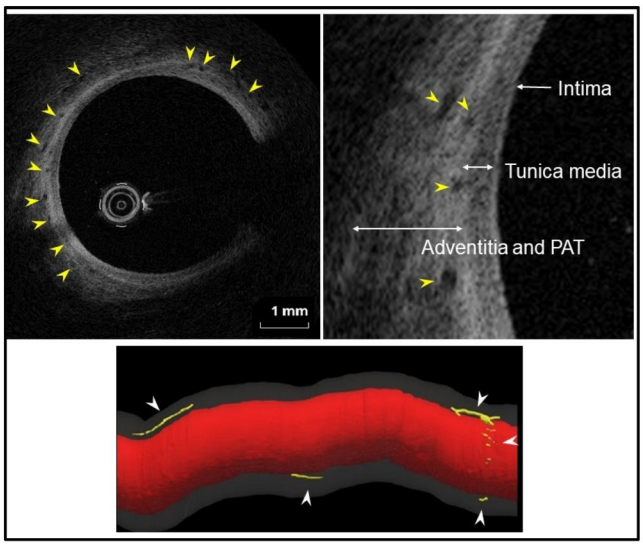
Summary

The vasa vasorum of the NT-SVG in vivo was investigated using FD-OCT. FD-OCT demonstrated abundant vasa vasorum (arrows) in the thick adventitia/perivascular adipose tissue layer of the NT-SVG. It suggests that the vasa vasorum in the NT-SVG is preserved in living humans after surgery and might contribute to long-term patency.



NT-SVG: no-touch saphenous vein graft, FD-OCT: frequency-domain optical coherence tomography.

Abstract

OBJECTIVES: One possible reason for the long-term patency of no-touch (NT) saphenous vein grafts (SVG) is the preservation of the vasa vasorum in the adventitia/perivascular adipose tissue (PAT). We investigated the vasa vasorum of the NT SVG in vivo using frequency-domain optical coherence tomography (FD-OCT), performed qualitative and quantitative analyses and compared them with the conventional SVG.

METHODS: An FD-OCT study was performed on 14 SVG at the postoperative coronary angiography 1–2 weeks postoperatively (NT group, $n = 9$; conventional group, $n = 5$).

RESULTS: Many signal-poor tubular lumen structures that can be recognized in the cross-sectional and longitudinal profiles, which indicates the vasa vasorum, were observed in the adventitial/PAT layer in the NT SVG. In contrast, the vasa vasorum were less abundant in the conventional SVG. The volume of vasa vasorum per millimetre of graft in the no-touch group was significantly higher than in the conventional group [0.0020 (0.0017, 0.0043) mm^3 and 0.0003 (0.0000, 0.0006) mm^3, $P = 0.023$].

CONCLUSIONS: FD-OCT showed abundant vasa vasorum in the thick adventitia/PAT layer of NT saphenous veins in vivo. In contrast, few vasa vasorum were observed in the conventional SVG.

Keywords: Coronary artery bypass grafting • Saphenous vein • No-touch saphenous vein graft • Optical coherence tomography

ABBREVIATIONS

CABG	Coronary artery bypass grafting
FD-OCT	Frequency-domain optical coherence tomography
NT	No-touch
PAT	Perivascular adipose tissue
SVG	Saphenous vein graft

INTRODUCTION

In 1996, Souza proposed the no-touch (NT) vein-harvesting technique, which involves harvesting a pedicled saphenous vein graft (SVG) with intact perivascular tissue without direct contact with the vein or high-pressure distension [1]. Excellent long-term patency has been reported [2–4]. Possible reasons include the preservation of vascular microstructures such as the endothelium, media, adventitia and perivascular adipose tissue (PAT) surrounding the vein [5–11]. In addition to physical support for the saphenous vein to prevent kinking, the PAT contributes to preserving the vasa vasorum and producing adipocyte-derived factors. Preservation of the vasa vasorum provides nutrients and oxygen to the vessel wall and could play a vital role in the improved performance of the NT-SVG [12–14]. Although it has been studied in specimens obtained during the operation and at autopsy, no reports have examined the vasa vasorum in living human SVG after coronary artery bypass grafting (CABG).

Frequency-domain optical coherence tomography (FD-OCT), which uses near-infrared light and optical interferometry, generates high-resolution cross-sectional images of tissue microstructure [15]. It has a high spatial resolution (10–15 μm), and microchannels in the FD-OCT are consistent pathologically with the vasa vasorum of the coronary arteries [16–19]. We investigated the vasa vasorum of NT- SVG in vivo using FD-OCT and performed qualitative and quantitative analyses of the vasa vasorum, comparing them to conventional SVG.

METHODS

Patients

This prospective study was approved by the institutional review board (# 23-123) and registered in the UMIN Clinical Trials Registry, which is officially recognized as a registry site that meets the International Committee of Medical Journal Editors criteria (UMIN 000047172).

Between 2022 and 2024, a total of 14 SVGs from 14 patients who underwent CABG at Jichi Medical University Hospital underwent FD-OCT to observe the vasa vasorum in vivo. Patients whose consent was obtained individually were included in the study and divided into 2 groups (NT group, $n = 9$; conventional group, $n = 5$). Patient selection was based on the presence or absence of adequate subcutaneous tissue. The patients without adequate subcutaneous tissue (skinny legs) were included in the conventional group to avoid leg harvest surgical site infection. The other patients had the NT technique. Regarding the nature of the saphenous veins themselves, preoperative leg ultrasonography and intraoperative findings confirmed the absence of varicose veins, large branches and intimal thickening/sclerosis due to inflammation and deep vein thrombosis. Homogeneity of the saphenous veins between the 2 groups before grafting was ensured.

FD-OCT was performed using coronary angiography 1–2 weeks after CABG.

Surgical technique

NT-SVGs were harvested using the technique described by Souza [1]. Briefly, preoperative ultrasound mapping of the saphenous vein was performed. NT-SVGs were harvested with an ∼2–3 mm margin of surrounding tissue on both sides, thereby avoiding direct grasping of the saphenous vein. We first perform a peripheral anastomosis during CABG. At the peripheral anastomosis, the NT-SVG often shrinks due to spasm. After harvesting, we attach a side branch (venous infusion line with an inner diameter of 2.28 mm) to the arterial line of the heart-lung machine, connect it to the NT-SVG and gently dilate with the pumping pressure instead of with high-pressure manual distention using a syringe.

Conventional SVGs were harvested by stripping them from their surrounding tissues and dilating them with normal saline with a syringe (5 or 10 ml) to overcome graft spasm. License holders of the Japanese Board of Cardiovascular Surgery performed SVG harvesting. The endoscopic vein harvesting technique was not applied. A total of 245 NT-SVGs were used for CABG between 2018 and 2024. Among them, 203 NT-SVGs were evaluated by coronary angiography or coronary computed tomography. Graft occlusion was observed in 2 grafts, and the patency rate was 99.0%.

Frequency-domain optical coherence tomography analysis

Routine coronary angiography was performed 1–2 weeks after CABG for postoperative evaluation. The Dragonfly OpStar FD-OTC imaging catheter (Abbott Cardiovascular, Chicago, IL, USA) and the SJM FD-OCT Imaging System (Abbott Cardiovascular) were used for 2-dimensional image analysis of the grafts. A 6-Fr guiding catheter was advanced to the SVG, and FD-OCT was performed. A total volume of 12–155 ml of contrast media at 4–5 ml per s was flushed, and blood was eliminated for 2–3 s. A 10-mm length of the

proximal SVG was analysed using automatic pullback devices at 40 mm/s.

We defined a signal-poor tubular lumen structure that could be recognized in cross-sectional and longitudinal profiles in the adventitia and PAT layer as the vasa vasorum, as described in previous studies [18, 19]. The luminal area of blood vessels was coarsely extracted from the FD-OCT images based on the region-growing method using open-source software, 3-dimensional Slicer (an open-source platform for image analysis, https://www.slicer.org/). The vessel shape was corrected manually using a pen tablet (DTK-2700; Wacom Co., Ltd, Kazo, Japan). The segmented vasa vasorum were separately exported to a stereolithography file. The volume of the extracted vasa vasorum was obtained using scFLOW v2023 (MSC Software Japan, Tokyo, Japan) that is capable of calculating the volume of an enclosed object described in a stereolithography file format. The vascular length was determined manually by measuring the distance between both edges of the extracted vasa vasorum. Given the volume and the length, an equivalent diameter (R) was gained from the following equation: $R = 2\sqrt{(V/\pi l)}$ (V, vascular volume; l, vascular length). The person responsible for the image analysis was blinded.

Statistical analysis

Continuous variables are presented as mean and standard deviation or medians (first and third quartiles), and categorical variables are presented as counts. The Student t-test or the Mann–Whitney U test was used to compare continuous variables, and Fisher's exact test was used for categorical variables. All statistical analyses were performed using EZR version 1.53 (Saitama Medical Centre, Jichi Medical University; https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics and clinical outcomes

The NT group included 9 NT-SVGs, and the conventional group included 5 conventional SVGs. Table 1 describes patient characteristics. Patients in the conventional group were older than those in the NT group. The other variables did not differ between the groups.

No hospital deaths or major complications occurred in either group. A leg harvest site infection was observed in 1 patient in the NT group. Postoperative coronary angiography revealed that all grafts were patent. The median follow-up period was 19 (16.5, 24.5) months. One case included planned endovascular treatment for a pre-existing iliac aneurysm 6 months postoperatively. Deaths, major adverse cardiovascular events or postoperative catheter coronary interventions were not observed during the follow-up period.

Frequency-domain optical coherence tomography findings of no-touch saphenous vein graft and conventional saphenous vein graft

Figure 1 shows cross-sectional images of the FD-OCT of an NT-SVG specimen obtained during the operation. The FD-OCT examination of this sample was performed immediately after the operation in vitro using the remaining part of the NT-SVG used for the grafting. Although the three-layer structure of the vein wall was obscured by vasospasm, it showed the signal-poor tubular lumen structures in the adventitia and the PAT layer, similar to those detected with postoperative optical coherence tomography.

Figures 2 and 3 show the findings of the FD-OTC performed 1–2 weeks after CABG. These are cross-sectional views (left) and enlarged images (right) of NT-SVG and conventional SVG. The FD-OCT scan showed a three-layered structure (intima, tunica media and adventitia/PAT) in both NT and conventional SVGs. The NT-SVG showed a thick adventitia/PAT layer. Many signal-poor tubular lumen structures recognized in the cross-sectional and longitudinal profiles, indicating the vasa vasorum, were observed in the adventitial/PAT layer of the NT-SVG (Fig. 2). In contrast, the vasa vasorum were less abundant in the conventional SVG (Fig. 3).

Three-dimensional rendering of the FD-OCT image demonstrated that many vasa vasorum ran longitudinally along the

Table 1: Patient characteristics

Variable	NT group ($n = 9$)	Conventional group ($n = 5$)	P- value
Age, years	65 ± 6	74 ± 5	0.01
Male	6 (67)	3 (60)	1
Comorbidity			
Body mass index	24 ± 5	22 ± 4	0.365
Hypertension	6 (67)	4 (80)	1
Hyperlipidaemia	8 (89)	4 (80)	1
Diabetes	6 (67)	2 (40)	0.58
Current smoking	2 (22)	1 (20)	1
Old myocardial infarction	4 (44)	0 (0)	0.221
Cerebrovascular disease	1 (11)	1 (20)	1
COPD	1 (11)	0 (0)	1
Haemodialysis	1 (11)	2 (40)	0.505
eGFR (ml/min)	46 ± 20	51 ± 38	0.744
LVEF (%)	59 ± 15	51 ± 13	0.362
ACS	1 (11)	0 (0)	1
Coronary lesions			
Left main trunk	3 (33)	3 (60)	0.58
3 vessels	4 (44)	2 (20	1
1 or 2 vessels	2 (22)	0 (0)	0.505
Number of anastomoses	2.7 ± 0.7	2.8 ± 0.4	0.712
Anastomosis site			1
Left circumflex branch	5 (56)	3 (60)	
Right coronary artery	4 (44)	2 (40)	
OPCABG	0 (0)	2 (40)	0.11
Concomitant AVR	1 (11)	0 (0)	1
Harvesting site (below the knee)	6 (67)	3 (60)	1
Medical therapy after the operation			
Beta blocker	9 (100)	5 (100)	1
ACE-I/ARB/ANRI	6 (67)	2 (40)	0.580
Calcium blocker	2 (22)	3 (60)	0.266
Mean blood pressure at the FD-OTC (mmHg)	83 ± 8	77 ± 13	0.285
SV graft/coronary ratio	2.1 ± 0.4	2.3 ± 0.6	0.342

Data are given as median and interquartile range or n (%).

ACE-I: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ANRI: angiotensin receptor-neprilysin inhibitor; ARB: angiotensin II receptor blocker; AVR: aortic valve replacement; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; FD-OTC: frequency-domain optical coherence tomography; LVEF: left ventricular ejection fraction; NT: no-touch; OPCABG: off-pump coronary artery bypass grafting; SV graft/coronary ratio: saphenous vein diameter/coronary diameter.

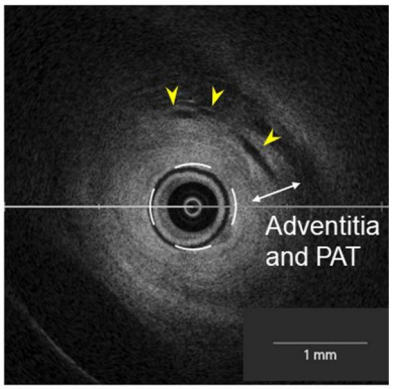


Figure 1: Cross-sectional image of frequency-domain optical coherence tomography of a no-touch saphenous vein graft specimen obtained during the operation. The frequency-domain optical coherence tomography examination of this sample was performed immediately after the operation in vitro using the remaining part of the no-touch saphenous vein graft used for the grafting. Although the three-layer structure of the vein wall is obscured by the spasm, signal-poor tubular lumen structures (arrows) can be recognized in the cross-sectional and longitudinal profiles in the adventitia and perivascular adipose tissue layer. PAT: perivascular adipose tissue.

adventitial/PAT layer of the NT-SVG. In contrast, few vasa vasorum were observed in the conventional SVG (Fig. 4).

Vasa vasorum volume in the no-touch saphenous vein graft and conventional saphenous vein graft

The equivalent diameter of the vasa vasorum was 100 (100, 200) μ, which was determined using the formula $R = 2\sqrt{(V/\pi l)}$ (V, vascular volume; *l*, vascular length) presented previously.

Figure 5 shows the volume of the vasa vasorum per millimetre of graft in each group. There was a significant difference in the volume of the vasa vasorum between the 2 groups [NT group, 0.0020 mm^3 (interquartile range, 0.0017–0.0043 mm^3); conventional group, 0.0003 mm^3 (interquartile range, 0.0000–0.0006 mm^3) $P = 0.023$].

DISCUSSION

Previous reports confirmed that NT-SVG preserved intact vasa vasorum in the specimens obtained during the operation and at

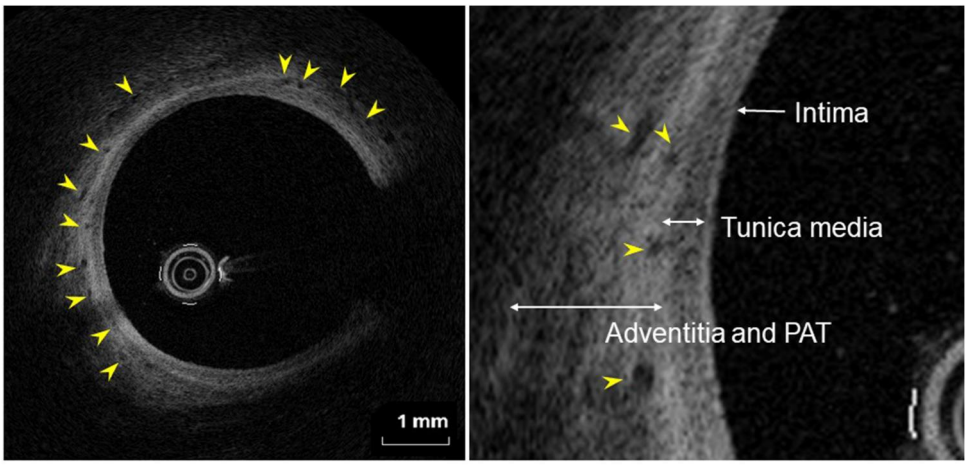


Figure 2: Cross-sectional images of the optical coherence tomography for the no-touch saphenous vein graft performed 1–2 weeks after coronary artery bypass grafting showing the three-layered structure (intima, media and adventitia/perivascular adipose tissue) and the vasa vasorum (arrows). Many vasa vasorum were found in the adventitial/perivascular adipose tissue layer. PAT: perivascular adipose tissue.

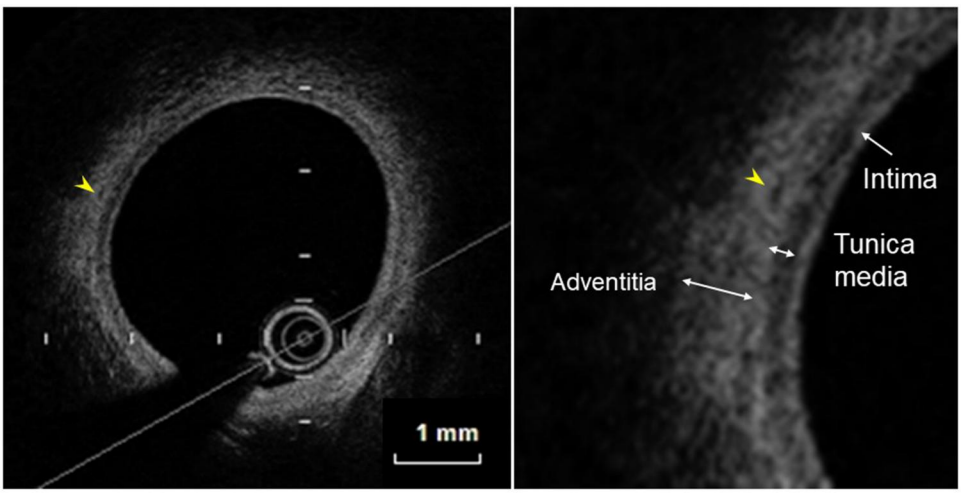


Figure 3: Frequency-domain optical coherence tomography of conventional saphenous vein graft performed 1–2 weeks after coronary artery bypass grafting shows a three-layered structure with little or no vasa vasorum (arrow).

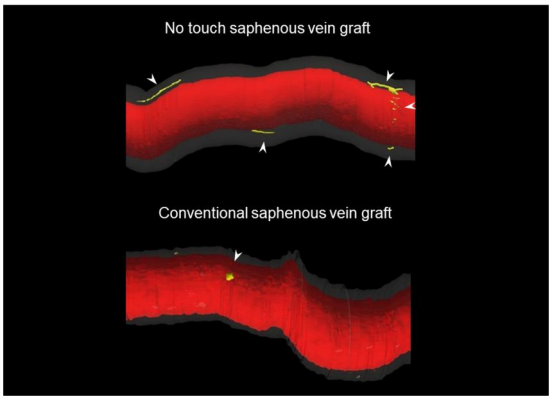


Figure 4: Three-dimensional rendering of optical coherence tomography images for vasa vasorum (arrow). The vasa vasorum run longitudinally along the adventitia in the no-touch saphenous vein graft, while few vasa vasorum are observed in the conventional saphenous vein graft. Upper image: no-touch saphenous vein graft; lower image: conventional saphenous vein graft.

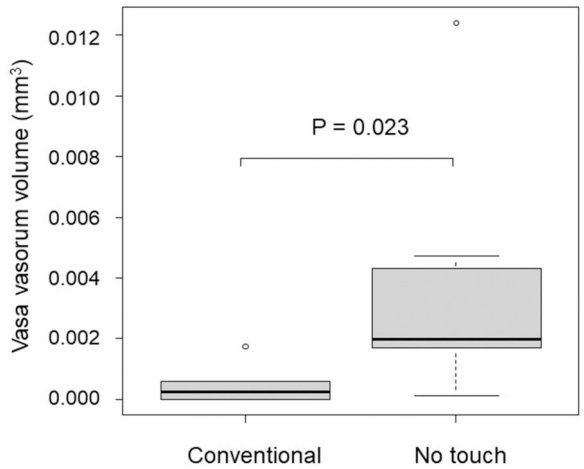


Figure 5: The vasa vasorum volume per millimetre of graft in the conventional saphenous vein graft and the no-touch saphenous vein groups.

autopsy microscopically [12–14]. In addition, Dreifaldt et al. confirmed the flow through the superficial network of vasa vasorum in an NT-SVG during the operation [20]. These findings suggest that functional vasa vasorum are present in the harvested NT-SVG at the time of the operation. However, whether the signal-poor tubular lumen structures detected by postoperative FD-OCT are vasa vasorum remains to be clarified. For example, it could be angiogenesis due to postoperative inflammation. To clarify this issue, we performed an FD-OCT examination of the remaining portion of the NT-SVG used in CABG. The same signal-poor tubular lumen structures as those observed on postoperative FD-OCT were also observed in the intraoperative specimen (Fig. 1). These findings indicate that the lumina detected by the postoperative OCT were the preserved functional vasa vasorum.

According to the description of the vasa vasorum of the saphenous vein reported by Kachlik *et al.* [21], the vasa vasorum approached the stem and tributaries of the saphenous vein from the surrounding adipose tissue at intervals of 1.5–2.5 cm; their smaller branches first passed the fascial compartments of the great saphenous vein and then entered the adventitia at intervals of 0.5–1.5 cm on both the stem and the largest tributaries of the saphenous vein. Our FD-OCT scans demonstrated that small vessels approximately 100 μ in diameter ran in the adventitia/PAT layer in the NT-SVG. The morphology of the vasa vasorum of the NT-SVG that we demonstrated in this study using FD-OTC (Figs. 2 and 4 upper) closely resembles that of the vasa vasorum shown in the cadaver specimen and the India ink injection technique in the intraoperatively harvested SVG reported previously [21]. These results suggest that FD-OTC may reveal the in vivo vasa vasorum after CABG. Although Kachlik *et al.* also reported a rich capillary network within the media in the veins [21, 22], the resolving power of FD-OTC enables delineation of the vasa vasorum network of the tunica media layer in this study.

Regarding the vasa vasorum of coronary arteries, recent studies using FD-OTC reported the association between vasa vasorum and atherosclerotic lesions [16–19]. In normal coronary arteries, the vasa vasorum are found primarily in the adventitia at its border with the media and running along the adventitial layer. Inflammation and atherosclerosis induce vessel wall thickening; under such circumstances, the vasa vasorum externae become angiogenic and expand deeper into the media and atherosclerotic plaques. Subsequently, they present a different morphology in atherosclerotic plaques as intraplaque neovascularization [23]. Taruya *et al.* reported that such neovascularization in plaques represents internally running vasa vasorum and a coral tree pattern, which is associated with plaque vulnerability [19]. Although the vasa vasorum externae ('healthy' vasa vasorum) of the coronary artery are morphologically similar to the vasa vasorum of NT-SVG running along the adventitia shown in this study, distinct qualitative differences exist between the arterial 'pathological' vasa vasorum (internal running or coral tree pattern) and the vasa vasorum of the NT-SVG. These morphological differences suggest that the luminal structures in the PAT of the NT-SVG detected by FD-OCT are not angiogenesis due to inflammation caused by the operation.

Three processes are responsible for venous graft failure: thrombosis, intimal hyperplasia and accelerated atherosclerosis. In NT-SVG, preserving the microvasculature, including the normal intima and medial smooth muscle cells, is thought to reduce thrombus formation and intimal hyperplasia [7–10]. However, it is unclear whether the vasa vasorum of the SVG are involved in the progression of vein graft atherosclerosis via mechanisms similar to those in the coronary arteries. It is also unknown whether the 'pathological' vasa vasorum have the same morphology as diseased coronary arteries. Future FD-OCT studies of NT-SVG during the remote period may clarify these issues, leading to a better understanding of the mechanisms of vein graft disease and the development of new treatment options.

This study has several limitations. (i) Because the diameters of the venous vasa vasorum are reported to be 11–200 μm [21] and the resolving power of FT-OTC is 10–15 μm, it should theoretically enable the detection of all vasa vasorum. However, owing to the inadequate removal of erythrocytes and the poor deep-depth resolution of FT-OTC, it may not delineate all of the vasa vasorum. In addition, OCT has a lower penetration depth than intravascular ultrasound; the penetration depth of intravascular ultrasound is 4–8 mm, whereas that of OCT is ∼2 mm. Therefore, OCT may not fully detect the vasa vasorum within the thick layer of PAT outside the adventitia. Therefore, the actual volumes of the vasa vasorum of the NT-SVG may have been higher than those obtained in this study. Regarding the penetration depth of OCT, comparative studies with intravascular ultrasound may

clarify the situation. (ii) The measurement length of the FD-OCT is 10 mm and is not measured over the entire length of the SV graft, which may not accurately reflect the overall volume of the vasa vasorum if there is little perivascular fatty tissue in this area. (iii) According to the original method described by Sausa *et al.*, the NT-SVG was harvested with ∼5 mm of PAT [1, 2]. We harvested NT-SVG with a smaller amount of PAT (2–3 mm) to prevent wound infections. Therefore, the volume of the vasa vasorum of the NT-SVG in this study may have been low. (iv) In this study, the vasa vasorum were observed in the early postoperative period. However, it is necessary to verify whether similar findings can be obtained in later postoperative periods. (v) This study was not a randomized study. Although we list baseline variables in groups in Table 1, they were not equivalent to controlling risk factors, which is the other limitation of this study.

CONCLUSIONS

The FD-OCT demonstrated abundant vasa vasorum in the thick adventitia/PAT layer of the NT-SVG in vivo. In contrast, few vasa vasorum were observed in the conventional SVG.

Funding

None declared.

Conflict of interest: none declared.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Akira Sugaya: conceptualization, data curation, formal analysis, investigation, project administration, writing the original draft; **Satoshi Uesugi:** data curation; **Masayuki Doi:** data curation; **Ryohei Horikoshi:** data curation; **Norihiko Oka:** project administration; **Shuta Imada:** formal analysis; **Kenji Komiya:** formal analysis; **Masanori Nakamura:** Supervision; Writing—review & editing; **Koji Kawahito:** project administration, Supervision; Writing—review & editing.

Reviewer information

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