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Intraoperative Detection of Intimal Lipid in the Radial Artery Predicts Degree of Postoperative Spasm

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Abstract

Background—The radial artery's (RA) tendency to spasm when used as a bypass graft may relate to features of the RA itself. We imaged RA conduits before and after CABG in order to characterize intimal abnormalities that might relate to the risk of spasm.

Methods—RA conduits from thirty-two CABG patients were imaged intraoperatively using catheter-based optical coherence tomography (OCT) and again on day 5 using 64-channel MDCT angiography. The change in luminal diameter between timepoints was measured in the proximal, mid and distal RA. "Spasm" was defined as focal or diffuse luminal narrowing to a diameter less than the target coronary. Lipid content in the RA was quantified by the degree of light attenuation on the OCT image.

Results—Postoperative spasm was diagnosed in 18 of 32 (56%) RA grafts with the distal RA showing the most severe change versus the mid and proximal portions (−24.1±43.2% vs. −15.3 ±40.7%, −9.0±42.5% change in diameter respectively, $p<0.01$). The degree of attenuation of the OCT signal produced by the RA was strongly correlated with % diameter change ($R=0.64$, $p=0.0005$) and was significantly more pronounced in grafts with spasm versus no spasm ($-1.97\pm0.61 mm^{-1}$ vs. $-0.81 \pm0.57 mm^{-1}$, $p<0.0001$). Histology confirmed lipid deposits in areas of RA with strong attenuation.

Conclusions—RA conduits otherwise considered acceptable for bypass grafting were often found by OCT imaging to have a substantial amount of lipid, which in turn strongly relates to the risk of postoperative spasm. Screening conduits based on characteristics of intimal quality may improve results following RA grafting.

Keywords

Computed tomography; optical coherence tomography; CABG; radial artery; vascular function

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Introduction

The superiority of the internal mammary artery (IMA) over the saphenous vein (SV) as a conduit for CABG (1) has prompted consideration of alternative arterial grafts such as the radial artery (RA). Widespread acceptance of the RA has been hindered by its tendency to develop post-operative spasm and early failure (2). It has been reported that the RA has a higher incidence of atherosclerosis and endothelial dysfunction compared to the IMA (3). Since the vascular endothelium is responsible for endogenous vasodilator production, differences in intimal quality between the RA and IMA might explain their disparate rates of postoperative spasm and failure. RA segments with atherosclerosis have been found to have increased spasticity *in vitro* (4). In addition, it has been noted that patients with peripheral vascular disease (and therefore at risk for atherosclerosis within the RA) are at increased risk for RA graft attrition (5). However, the link between intimal disease in the RA and early graft spasm *in vivo* has never been established directly using clinical evidence.

Catheter-based optical coherence tomography (OCT) provides real time visualization of the vascular intima at near histological resolution. OCT can be reliably employed to characterize the presence of atherosclerosis and to provide precise measurements of changes in vessel diameter. As a result, we have used OCT as an intraoperative quality assurance tool to screen for intimal pathology (6) and spasm (7) within RA conduits. In addition, transmural optical attenuation of the OCT signal can further quantify RA vessel quality. Combined with morphological imaging, evidence of heightened signal attenuation on OCT is highly sensitive for differentiating lipid-laden plaque from fibrous plaque with little lipid content (8). The ability to characterize atherosclerotic plaques may help identify a RA with more severe underlying endothelial disease than expected. Because the link between endothelial disease and vasospasm is well known (9), we hypothesized that identifying lipid plaque within RA conduits using intraoperative OCT imaging would increase the risk of postoperative spasm of the RA graft.

Methods

Subject enrollment

Following IRB approval (UM protocol #H25350), patients undergoing isolated CABG and scheduled to receive both RA and SV grafts were eligible for inclusion. Patients were excluded for creatinine >2.0 mg/dl, refusal or inability to obtain informed consent, abnormal oximetric Allen's test (10), hemodialysis requirement, uncontrolled diabetes, or Raynaud's disease.

Surgical technique

RA and SV grafts were harvested by a single experienced technician (>500 endoscopic harvests), then flushed with heparinized saline and stored in a plasmalyte solution containing glyceryl trinitrate and verapamil (11). RA's were procured using standard pedicled technique by a single harvester (12). A single surgeon performed CABG off-pump via median sternotomy. Each patient received RA, IMA and ≥1 SV grafts. RA grafts were sewn to coronary targets with an upstream stenosis >80%. Blood flow was assessed in each graft with and without occlusion of the native target coronary artery using a transit-time flow meter (Medistim, Inc., Minneapolis, MN) to monitor for evidence of competitive flow (13).

OCT imaging and analysis

RA conduits were imaged at a 1mm/sec pull-back rate via a 1F OCT catheter (ImageWire, LightLab Imaging, Westford, MA) *in situ* using an upper arm tourniquet and infusion of heparinized saline to clear blood from the artery, as previously described (6). SV's were imaged in a similar manner *ex vivo* after harvest. Attenuation of light emitted by the OCT probe was quantified at proximal, mid, and distal areas in each RA using automated image processing

software (LightLab Imaging, Westford, MA) (Figure 1). Lipid in the vessel wall was quantified as the degree of OCT signal attenuation (mm^{-1}) by calculating the slope of a plot relating light intensity (arbitrary units) to the depth of signal penetration (mm), where a more negative attenuation value was interpreted to represent higher lipid content (8). Additional measurements of intimal and medial thicknesses (used to determine intimal-medial thickness (IMT) and intima-media ratio (IM ratio)) (14), and baseline luminal diameter were made at proximal, mid, and distal points.

Histological examination

Biopsies were obtained from discarded regions of interest in RA's to confirm the presence of lipid. The region of biopsy excision was marked externally at the location of the catheter, visualized by gross examination of the rotating infrared light at the catheter tip. This allowed exact calibration of the OCT images to their corresponding histopathological sections. These "image-guided" biopsies were embedded and frozen in cutting compound (Tissue-Tek O.C.T., Redding, CA), then sectioned at 5 μm and analyzed using Oil Red O staining to identify areas of lipid.

CT angiography

Chest CT angiography (CTA) was acquired via 64-MDCT scanner (Philips Medical Systems) on postoperative day 5 (POD5) and interpreted by a thoracic radiologist using axial and reconstructed curved planar images. All RA grafts had luminal diameter measurements made at proximal (1 cm distal to aortic anastomosis), mid (exact middle of graft) and distal (1 cm proximal to coronary anastomosis) locations. Spasm was defined as a patent graft with a luminal diameter less than that of its coronary target, and further characterized as "diffuse" or "focal" when present in >50% versus <50% of the graft length, respectively. Angiographic "string sign" was defined as diffuse narrowing of the graft to <1 mm, as previously described (2). Degree of postoperative spasm was quantified by comparing the luminal diameter measurements from intraoperative OCT imaging to CTA measurements obtained at registered RA portions on POD5. Change in SV graft diameter between these same timepoints was used as a control.

Statistics

The primary endpoint of this study was to define the relationship between RA intimal lipid content (i.e., "light attenuation") and degree of luminal narrowing within the graft (% diameter change measured intraoperatively versus POD5) early after CABG. The relationships between % diameter change and other experimental variables, both continuous and categorical, were analyzed using Pearson's correlation coefficients and student's t tests, respectively. Intra-conduit differences in light attenuation, IM ratio, IMT, % diameter change, and baseline RA diameter were compared via repeated measures one-way ANOVA, with Bonferroni's multiple comparison post test. Statistical analysis was performed using the InStat statistical package (GraphPad Software, Inc., San Diego, CA).

Results

Patient and graft characteristics

From March 2006 to June 2007, 32 patients the received RA grafts were enrolled. Ten patients undergoing RA grafting during this study interval were excluded due to elevated creatinine (n=6) and failure to obtain consent (n=4). Baseline patient characteristics are provided in Table 1. All patients received perioperative nitrates and none received intraoperative vasopressors. Mean values for light attenuation, IMT, IM ratio, and baseline diameter were not significantly

different when comparing measurements taken at proximal, mid, and distal portions of each RA.

Graft Assessment

Intraoperative OCT examinations were performed on each RA and SV with an average time of 2.7±0.2 min/conduit. Biopsies were obtained from discarded RA portions registered against OCT images that showed enhanced signal attenuation. On four occasions, a portion of RA demonstrated a signal attenuation slope that was steeper than $-1.5\ mm^{-1}$. The presence of lipid was confirmed using histological techniques in specimens obtained from each of these RA biopsies (Figure 2).

CT angiography was completed in all patients on POD5. Graft occlusion was noted in 0/32 (0%) RA's and 2/32 (6%) SV's. The average postoperative luminal diameter was 2.0±0.8 mm for RA's, which represented a mean decrease of −16.1±39.1% compared to the diameter measured intraoperatively by OCT. This decline in diameter was sufficient to diagnose post-operative spasm in 18/32 (56%) RA's. Spasm was "diffuse" in 9/18 (50%) and "focal" in 9/18 (50%) grafts. Post-operative spasm was not noted in any SV grafts, with most showing an increase in postoperative diameter versus baseline (+50.7±42.5% increase).

Factors related to RA narrowing

The mean postoperative % diameter change was −9.0±42.5%, −15.3±40.7%, and −24.1±43.2% for the proximal, mid and distal RA portions, representing a significant difference in the degree of narrowing within proximal versus distal RA segments ($p<0.01$). The degree of luminal narrowing on CT angiography showed a strong correlation with the average RA light attenuation value (i.e. slope of the attenuation vs. depth of penetration of the signal) calculated via OCT imaging ($R=0.64$, $p=0.0005$, Figure 3). Baseline RA diameter also showed an inverse correlation to postoperative luminal narrowing, but the relationship was less robust ($R=-0.38$, $p=0.03$). RA's showing post-operative spasm demonstrated a greater mural signal attenuation than non-spastic RA's (-1.97 ± 0.61 vs. $-0.81\pm0.57 mm^{-1}$, $p<0.0001$). None of the other imaging data obtained by OCT (e.g., IMT, IM ratio) were found to relate to postoperative luminal narrowing. Preoperative use of lipid-lowering agents was found to reduce the % diameter change compared to those not actively treated with statins (−5.5±31.9 vs. −62.2 ±35.5%, $p<0.01$). None of the other clinical characteristics analyzed showed a relationship to spasm (age, BMI, EF, target size, graft blood flow, degree of native coronary stenosis, sex, smoking history, current smoking, diabetes, hypertension, PVD, medication use).

Discussion

As an arterial conduit, the RA is accustomed to the arterial pressure and pulsatility that occurs within coronary artery bypass grafts, providing it with a theoretical advantage over the saphenous vein (15). Yet the RA is utilized as a conduit in less than 20% of CABG procedures performed in the US due mainly to concerns about the risk of early failure and spasm after grafting (2). Well-controlled prospective trials have advanced our knowledge about the clinical risk factors for RA spasm (5). However, the impact of RA quality on outcomes after grafting remains undefined. Prior evidence suggests that endothelial disease in the RA increases its spasticity i*n vitro*. In addition, the risk of RA string sign development after CABG is increased in patients with coexisting peripheral vascular disease (5). As a result, it has been hypothesized that atherosclerosis may be an underappreciated risk factor for RA bypass graft spasm (4). In our study, clinically applicable tools (e.g. catheter-based OCT and CT angiography) were used to measure the intimal quality of RA conduits prior to grafting and define spasm after grafting as a direct means of investigating this hypothesis. The results of our study provide the first

clinical evidence to support a relationship between RA intimal quality and its risk of spasm when used as a bypass graft.

If the traditional angiographic criteria of "string sign" or diffuse narrowing to <1 mm were used in our study, we would have noted a similar incidence of RA spasm (13%) as described in previous reports (2). However, using a more physiologic criterion of spasm (i.e. change in RA diameter likely to yield a restriction in blood flow), we diagnosed spasm in a majority of RA's (but not SV's or IMA's). The strength of this type of definition is that it has been shown by Fitzgibbon et al. to correlate with long term graft patency and patient outcome (16). The high incidence of RA spasm was unexpected because our cohort was felt to be at low risk based on previously reported clinical risk factors: low incidence of diabetes and peripheral vascular disease, no vasopressor use, placement of each RA graft onto a coronary artery target with proximal stenosis ≥80% and no evidence of competitive flow when measuring flow within the graft with and without native vessel occlusion. Our broader definition of spasm takes advantage of the high precision of MDCT for measuring of the luminal diameter within the body of bypass grafts (17). We measured the diameter of each RA conduit intraoperatively with OCT imaging in order to confirm that luminal narrowing measured postoperatively was indeed a dynamic change and therefore consistent with spasm, further strengthening our definition.

An additional finding of intraoperative OCT imaging was the striking variability in the mural attenuation of infrared light in RA that otherwise appeared highly acceptable for use as bypass conduits. It has been previously shown (8), and confirmed in our analyses of discarded RA segments, that this attenuation of the OCT signal is caused mainly by lipid. For each RA, we determined the ratio of light intensity with the depth of signal penetration in order to quantify RA lipid. This parameter, the slope of signal attenuation, proved to be a strong predictor of the degree of spasm noted on day 5 after CABG. Our data also corroborates the findings of others indicating that spasm is more likely when a distal as compared to proximal portion of the RA is used for grafting (18) and that lipid-lowering agents are likely protective against spasm (19), but none of these factors demonstrated as strong of a relationship as the signal attenuation within the RA. The amount of plaque, defined by intimal-medial thickness and IM ratio on RA imaging, did not show a relationship to the degree of luminal narrowing after grafting. This suggests that the prognostic value of OCT imaging is derived more from its ability to differentiate stable, fibrous lesions from lipid-laden plaque that are associated with foam cells and active inflammation. The increased tendency for lipid-laden RA to spasm may be explained by more marked endothelial dysfunction, which is associated with deficient local production of vasodilators (e.g. nitric oxide, prostacyclin) and unopposed constriction of the medial layer (20).

These findings have strong clinical relevance because they suggest that OCT imaging could be used to quantify the lipid content of RA *in situ*, prior to excision from the arm, and therefore used to select RA for harvest that are predicted to have the lowest likelihood of spasm for grafting. In addition, our protocol provides a unique clinical model for addressing the broader controversy how intimal disease, identified *a priori*, affects vessel function when placed into a provocative surgical environment.

Our study has several limitations. The attenuation of the signal seen on OCT imaging of the RA may have been confounded by factors other than intimal lipid. Blood cells lead to scattering of the light which strongly attenuates the reflected signal (21). However, *in situ* OCT examinations were performed when the RA was exsanguinated and flushed with crystalloid, minimizing the chance that residual blood would affect our results (6). Calcium also attenuates the OCT signal, albeit to a lesser extent than lipid or blood (8). Although calcium is a common component of an atherosclerotic plaque, it does not signify an active inflammatory process to the extent that lipid does, potentially confounding our hypothesis about endothelial disease and

RA graft spasm. Quantifying the back-scattering of light in addition to attenuation has been described as a method to help discern calcium from lipid (8). Attenuation of the OCT signal provides clinically meaningful information even without this further analysis because it is generally accepted that calcium deposition hinders vasodilation and is a contraindication to use of the RA as a bypass graft in CABG (22). Additionally, our previous OCT analyses of RA conduits have noted that calcific lesions are much more infrequent than lipid-laden ones (23). Our study was also limited by its small size and lack of long term follow-up. As a result, it was not statistically powered to be able to adequately adjust for clinical variables that could have influenced the results. Without the use of conventional angiography or long term follow-up in our protocol, we were not able to establish the pathogenecity of early RA spasm by demonstrating a relationship to graft blood flow or an influence on patient morbidity and mortality. Of note, prior studies have shown that early postoperative RA spasm resolves at 6 months (24). Ongoing studies on a larger cohort of patients receiving a RA graft will help to address these limitations. Finally, our study does not prove that the intimal abnormalities identified preoperatively are causally related to spasm in the RA graft postoperatively. Areas of lipid deposition might serve as a marker for underlying smooth muscle cells expresssing a phenotype that is predisposed to develop spasm (25). Further studies are required to define the roles of the intima versus media on RA graft function.

In conclusion, this prospective cohort study demonstrated that the OCT signal attenuation of RA conduits, suggested by this and prior studies to be a measure of intimal lipid content (6, 8), is a strong predictor of the degree of spasm that is likely to develop during the early postoperative period. Sequential imaging of each RA using intraoperative OCT and postoperative 64- MDCT angiography provides a means for quantifying more moderate degrees of RA spasm with a sensitivity that has not previously been described. In addition, we quantified attenuation within the portions of RA vessel that were actually used for bypass grafting, another critical feature of our protocol for establishing the direct link between the intimal lipid content and the risk of spasm. Ongoing studies will investigate the role of OCT imaging as a method for screening conduits that have the greatest potential for long-term patency.

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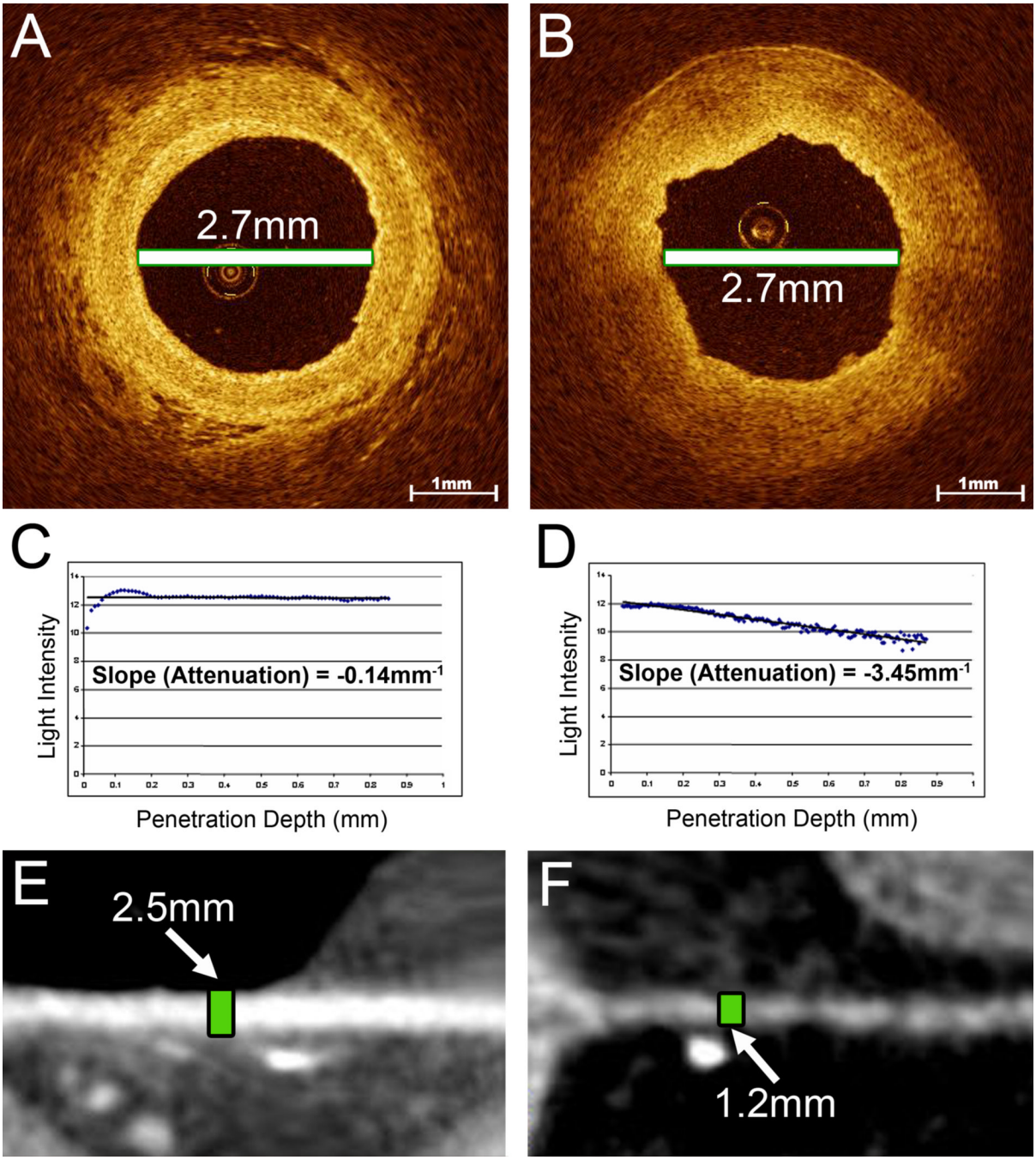

Fig. 1.

OCT attenuation values and postoperative luminal narrowing on 64- MDCT. Lipid in the intimal wall produces increased shadowing on OCT imaging (A, B), which yields more negative attenuation slopes via image processing (C, D). Degree of postoperative luminal narrowing was calculated by comparing *in situ* diameter measured via OCT (A, B) and postoperative day 5 diameter measured via 64 -MDCT (E, F). RA's with more negative attenuation slopes (i.e., higher intimal lipid content) showed more significant postoperative luminal narrowing.

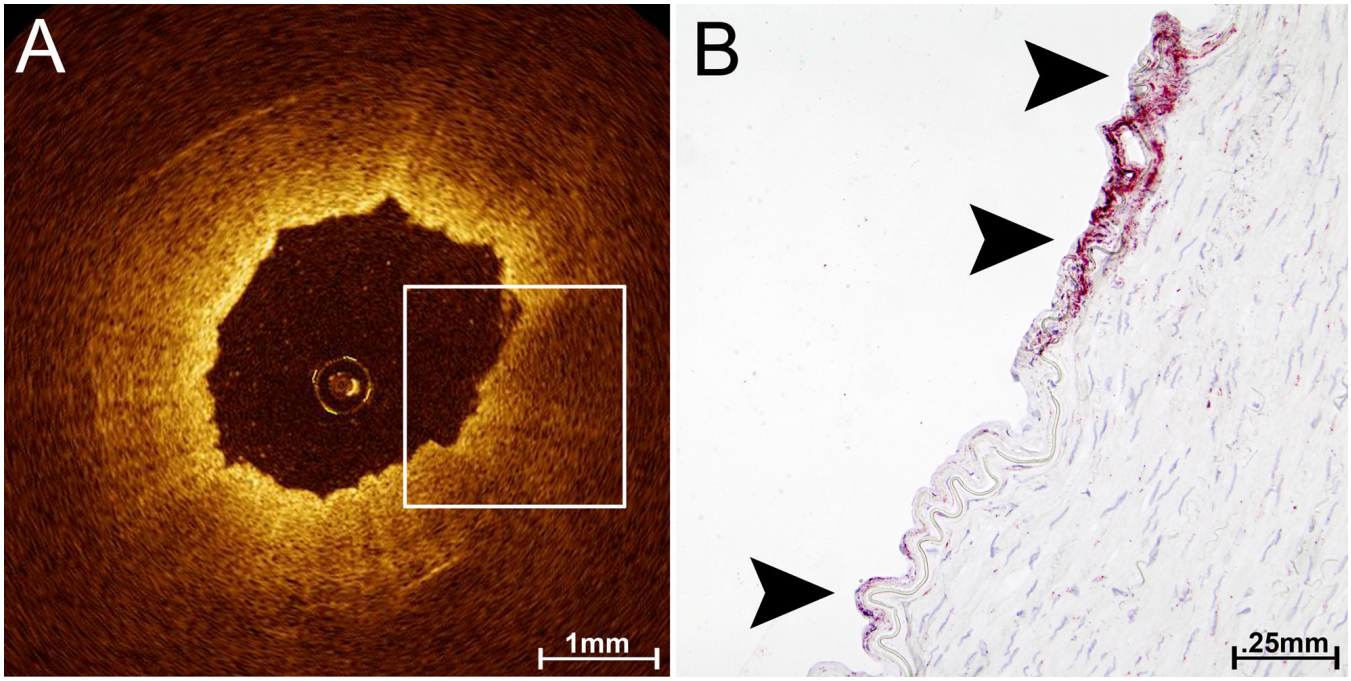

Fig. 2.
Detection of focal lipid via OCT and histological comparison. The OCT image (A) shows focal areas of increased light attenuation secondary to intimal lipid deposition, which was confirmed via O Red O staining on a registered histological section.

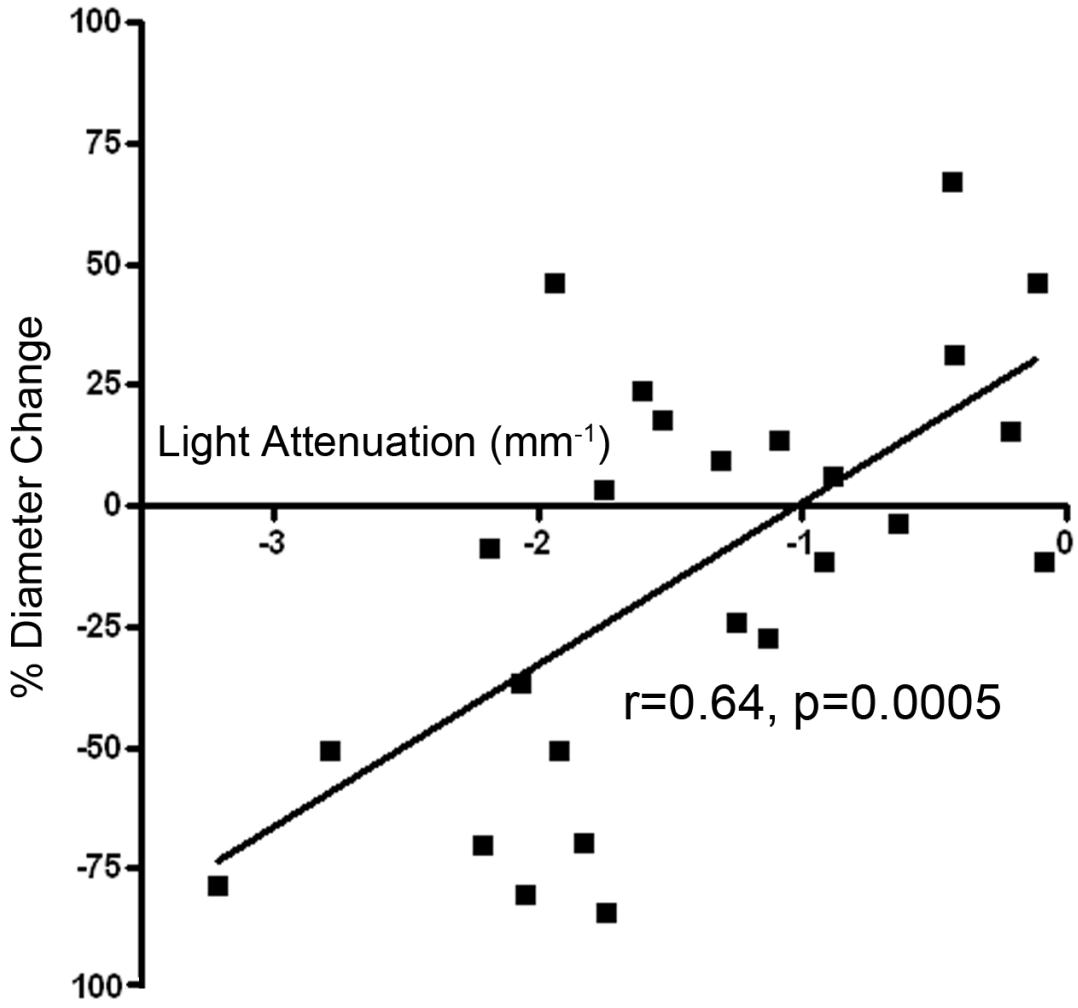

Fig. 3.
Relationship between OCT light attenuation and post-operative RA diameter change. A more negative light attenuation value suggests increased lipid deposition in the RA intima and is correlated with greater post-operative luminal narrowing.

Table 1

Patient and Graft Characteristics

Categorical Variables	
Characteristic	**Number of Patients (%)**
Male sex	28 (87.5%)
Smoking History	24 (75%)
Current Smoking	11 (34.4%)
Diabetes mellitus	12 (37.5%)
Hypertension	29 (90.6%)
Peripheral vascular disease	5 (15.6%)
ERAH	13 (40.6%)
Beta-blockers	25 (78.1%)
ACE-inhibitor	15 (46.9%)
Lipid-lowering agent	26 (81.3%)
Continuous Variables	
Characteristic	Mean±SD
Age (yrs)	63.4±9.4
Body-mass index	29.3±6.3
Ejection fraction (%)	40.4±15.5
Graft Flow (ml/min)	46.7±23.2
Pulsatility index	2.4±1.1
Native target size (mm)	1.9±0.4
Native stenosis (%)	81.7±12.7
RA IMT (mm)	0.35±0.08
RA IM ratio	0.37±0.21
RA intraoperative luminal diameter (mm)	2.48±0.48

ERAH, Endoscopic radial artery harvest; ACE, angiotensin-converting enzyme; IMT, intimal-medial thickness; IM, intimal-medial; RA, radial artery