Article

Direct Blood Flow Measurements in a Free RPE-Choroid Graft with Phase-Resolved Doppler OCT

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Purpose: We directly demonstrated the revascularization in a free retinal pigment epithelium (RPE)-choroid graft with direct blood flow detection by experimental phase-resolved Doppler optical coherence tomography (PRD-OCT).

Methods: Seven patients with age-related macular degeneration underwent an RPE-choroid graft translocation in a prospective institutional cohort study. Spectral domain optical coherence tomography (SD-OCT) was used to measure the revascularization stage. With PRD-OCT the presence of flow was imaged postoperatively.

Results: The PRD-OCT confirmed flow in three patients when SD-OCT indicated the afferent vessel ingrowth stage, and in all seven patients when the SD-OCT indicated the efferent vessel ingrowth stage.

Conclusions: The PRD-OCT study was able to detect the presence of blood flow in a free RPE-choroid graft. The PRD-OCT findings directly confirmed the revascularization that was otherwise based on the more circumstantial evidence provided by SD-OCT images and angiography.

Translational Relevance: The use of both techniques to monitor the revascularization process in a free graft in patients are an interesting example of replacing more invasive by noninvasive techniques. There is potential future use of PRD-OCT for the visualization of vascularization patterns in other pathologies.

Introduction

Exudative age-related macular degeneration (AMD) is the leading cause of irreversible legal blindness in elderly patients in the industrialized world.¹ Exudative AMD is predominantly treated with antivascular endothelial growth factor (anti-VEGF), which has proven to preserve or improve visual acuity (VA) in the vast majority of patients.² There are patients, however, who do not benefit from this treatment. These include patients with fibrosis under the macula,³ retinal pigment epithelium (RPE) tears,⁴ patients who do not respond to anti-VEGF therapy,⁵ or patients with (large) older hemorrhages that cannot be treated with recombinant tissue plasminogen activator (rtPA).⁶ For these patients, an RPE-choroid graft surgery is an alternative

treatment option. During this surgery neovascular membranes and fibrotic tissue located beneath the macula are removed and replaced by a free autologous RPE and choroid graft obtained from a location in the midperiphery.^{7,8}

We hypothesize that best functional outcome for this treatment relates to a preserved neuroretina in the macula and revascularization of the graft. As described previously, spectral domain optical coherence tomography (SD-OCT) allows the visualization of structural tissue changes during three well-established revascularization stages in an RPE-choroid graft shortly after surgery.⁹ The first step is the serum imbibition stage: small vessel lumina are visible inside the graft, and the graft appears to be very thin. In this early phase after transplantation, plasma exudes from the recipient site's damaged arteries and veins, fills the lumina of the graft vessels, and supposedly supports

graft-tissue metabolism. Serum imbibition is a name used for this process in free dermal skin grafts to describe this passive filling of vessel lumina.¹⁰ The second step is the afferent vessel stage: the number and the mean diameter of the vessels increase and the graft becomes thicker. The third step is the efferent vessel stage: the thickness of the graft and the diameter of the vessels may slightly decrease while the number of vessels may slightly increase. This is accompanied by a change in gray shading of the vessel lumina, suggesting blood flow.⁹ This observation of the three revascularization stages with SD-OCT was confirmed previously by fluorescein angiography (FA) and indocyanine green angiography (ICGA).⁹ Postoperative follow-up by SD-OCT reduces the need for more invasive techniques as FA and ICGA.^{11,12} However, all three methods provide indirect, circumstantial evidence for revascularization. In angiography, it is uncertain at which depth the vessels stain and with SD-OCT repeated measurements are necessary. Whilst SD-OCT is an indirect method to detect blood flow, a direct detection is desirable. Therefore, we analyzed the graft perfusion during the revascularization process with a new noninvasive, but direct method: phase-resolved Doppler optical coherence tomography (PRD-OCT), which can detect flow in one exam.

Recently, OCT technology has been improved with the introduction of optical frequency domain imaging (OFDI), which also is known as swept-source OCT.¹³ The advantage of OFDI over SD-OCT is the lower signal decay at increased imaging depth, and a reduced susceptibility to motion artifacts.¹⁴ In practice, this provides a large imaging depth range, which is especially interesting for the imaging of thick tissue samples. Further, the introduction of broadband light sources at wavelengths of approximately 1 μm have tremendously improved the visualization of choroidal structures due to the lower light scattering in the retina, compared to traditional 850 nm light sources.^{15,16} The deep tissue penetration of 1 μm OCT is of particular interest for the investigation of diseases, such as exudative AMD, whose pathogenesis begins in the subretinal vascular network.¹⁷ The imaging of vascular networks with OCT is further strengthened by the use of PRD-OCT techniques. In this functional extension of the standard OCT technique, blood flow is detected from phase changes in the OCT signals within successive measurements. These phase changes are caused by the Doppler effect of moving intravascular particles, such as erythrocytes and leukocytes.^{18–20} We hypothesized that PRD-OCT, based on OFDI

equipped with a 1- μm light source, is an ideal tool for the investigation of blood flows that are deeply embedded within RPE-choroid grafts. Therefore, an experimental prototype of such an instrument was constructed in our lab, and it already has been used to demonstrate the possibility of detecting blood flow within RPE-choroid grafts.²¹

In this study, seven patients were examined during an extended postoperative follow-up to investigate the validity of PRD-OCT for the detection of blood flow after RPE-choroid transplantation surgery, and to directly confirm the revascularization steps that have been detected from tissue structure changes in a previous SD-OCT study.⁹

Methods

Patients

Seven patients with exudative AMD who were ineligible for (further) anti-VEGF or other treatment were included in this prospective cohort study. Patients could be included if they were nonresponders to anti-VEGF treatment (i.e., if they had a visual loss of ≥ 15 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart after at least three anti-VEGF injections), if they had a massive submacular hemorrhage that was no longer eligible for rtPA injection (i.e., existing for ≥ 2 weeks),⁶ a fibrotic macular scar, or an RPE tear. All examinations and surgical procedures were performed at the Rotterdam Eye Hospital (REH; Rotterdam, The Netherlands). All patients provided informed consent for the surgical procedure, and for pre- and postoperative examinations, in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Medical Ethical Committee of the Erasmus University (Rotterdam, The Netherlands), Dutch CCMO register number NL 26968.078.09.

Surgery

All patients underwent a full-thickness translocation of autologous midperipheral RPE, Bruch's membrane, choriocapillaris, and choroid (RPE-choroid graft). As described previously,⁹ one of two possible surgical procedures was performed: one with the creation of a small retinectomy in the raphe followed by the positioning of a midperipheral graft under the macula using a bent forceps²² ($n = 5$), or another in which the free graft of RPE and choroid could be dragged over the macula area after the creation of a large (180°) peripheral temporal

retinotomy¹¹ ($n = 2$). At the end of the surgery, silicone oil (5000 centistokes [cSt]) was used as tamponade. All surgical procedures were performed by one surgeon (JvM). The silicone oil was removed in a second procedure approximately three months after the first surgery. Lensectomy or phacoemulsification was performed during the first procedure in phakic patients ($n = 3$). Insertion of the intraocular lens was performed during second surgery.

Visual Acuity

To test visual function, the best corrected VA was measured preoperatively, and at 3 and 6 months postoperatively on an ETDRS chart. The VA measurements were reported as number of letters. Conversions to logarithm of minimal angle of resolution (logMAR) were done according to Holladay's conversion method in which finger counting at 60 cm was transposed to logMAR 2 and hand motion to logMAR 3.²³

SD-OCT and PRD-OCT

To image the tissue structure of the graft, all patients were scanned on a regular basis by SD-OCT pre- and postoperatively, as previously described.⁹ To directly detect blood flow in the graft, all patients were imaged with PRD-OCT.

Our group recently developed an experimental OFDI system to perform clinical studies in ophthalmology.²¹ The system uses a swept-source laser in the 1- μm wavelength range (Axsun Technologies, Inc., Billerica, MA, USA), which operates with a 100-kHz A-scan rate. The axial resolution was measured to be 6.5 μm in air (4.7 μm in tissue) and the lateral resolution was 10 μm . The PRD-OCT images of the blood flow in the grafts were created by calculating the phase-difference on the interference between sample and reference arm light for succeeding A-scans. Considering a relatively steep angle of incidence of the OCT light with the blood flow direction in the retina (Doppler angle),²⁴ the minimum detectable flow velocity ranged from 5.6 mm/s for a 70° Doppler angle to 110 mm/s for a 89° Doppler angle.²¹ This limited the visualization of blood flow to the larger vessels with a relatively high blood flow velocity and a minimal vessel diameter of 60 μm . Small blood vessels of the choroidal (micro-) vasculature, therefore, could not be detected. In Figure 1, an example is given of PRD-OCT of the choroid in a healthy subject. This Figure shows that, although PRD-OCT gives sparse information on the flow, large

sections of several blood vessels can be visualized clearly. In this study two PRD-OCT measurement protocols were used. The first protocol consisted of a single B-scan measurement over a line of 2.2 mm in width on the retina for which 2000 A-scans were acquired. The acquisition time for this protocol was 20 ms. The second protocol measured a three-dimensional data volume consisting of 250 single B-scans with 2000 A-scans/B-scan over a retinal area of 2.2 mm in width and 4.1 mm in length. The acquisition time for a three-dimensional volume was 5.0 seconds. During a single patient visit several single B-scans and three-dimensional volume datasets were acquired for which the total measurement duration was never more than 30 minutes. The three-dimensional datasets were processed afterwards into flow en face images by integrating the absolute phase-difference values over depth to visualize the distribution of the sparse flow signals in the vascular network of the graft. All patients were repeatedly measured postoperatively with PRD-OCT, the last measurement ranging from three months up to one year after surgery (timing of examination for each patient is summarized in [Supplementary Table S1](#)). During each visit several horizontal single B-scans were taken at various locations in the graft around the macula. In the presented images ([Fig. 2A](#)), 4 to 10 B-scans were averaged to improve the image quality. Additionally, several volume scans were made to evaluate the perfusion of the graft over a large area. The presence or absence of blood flow was registered for every visit and compared to the revascularization steps as observed in the structural imaging with the SD-OCT ([Supplementary Table S2](#)).

Results

Patients

The mean age ($\pm$ standard deviation [SD]) of the seven patients was 80.1 ± 13.9 years. All patients had exudative AMD. Indication for surgery in two patients (N.3 and N.4) was a submacular hemorrhage and an RPE tear; both were on anti-VEGF therapy, and patient N.4 received rtPA in an earlier surgery. Patient N.1 had a hemorrhage after one anti-VEGF injection, a fibrotic reaction, and posterior uveitis. Patient N.2 presented with a new submacular hemorrhage after anti-VEGF and rtPA surgery. Patient N.5 had a residual hemorrhage and fibrosis after anti-VEGF injections and rtPA surgery. Patient N.6 presented with an RPE tear and macular pucker.

Figure 1. PRD-OCT measurements of the choroid in a healthy subject. A three-dimensional dataset was acquired from the center of the macula including the fovea. (A) A PRD-OCT intensity B-scan showing the retinal and choroidal structures. The choroidal depth over which flow was evaluated is outlined by *blue* and *green* lines. (B) A PRD-OCT bidirectional flow B-scan from the location of (A). Blood flow is visualized as *white* and *black* areas for flow directions that are respectively towards and away from the OCT instrument. Tissue without blood flow is displayed in *gray* and locations above the inner limiting membrane (i.e., in the transparent vitreous) shows random noise. In the choroid several vessels can be distinguished. (C) A PRD-OCT intensity B-scan of the retina with an overlay of the absolute flow in *red*. (D) An IR-image of the retina of the healthy subject showing the surface area where the three-dimensional dataset was obtained demarcated with a *white* box. (E) An en face flow image of the absolute PRD-OCT signals which shows flow in the choroid for several blood vessels with high blood flow velocities. The blood flow is visualized in *black* and marked by *white* ovals.

Patient N.7 was a nonresponder to anti-VEGF therapy. Four patients were on anticoagulants before surgery (three patients on platelet aggregation inhibitors, one patient on anti-coagulants).

Visual Acuity

The VA at baseline ranged from 20/87 to 1/300 (0.64–2.8 logMAR), with a median of 1.26 (20/364) and a mean of 1.32 (SD $\pm$ 0.72) logMAR. The VA after 3 months ranged from 20/42 to 20/418 (0.32–1.32 logMAR) with a median of 0.84 (20/138) and a mean of 0.88 (SD $\pm$ 0.31) logMAR. Mean improvement was 11.9 VAS (visual acuity score) letters, with a median of 5 letters. The VA after six months ranged from 20/42 to 20/276 (0.32–1.14 logMAR) with a

median of 0.8 logMAR (20/126) and a mean of 0.73 logMAR (SD $\pm$ 0.26) logMAR. Mean improvement was 20.4 VAS letters with a median of 15 letters. The characteristics of and exact number of letters read by each patient are summarized in [Supplementary Table S1](#).

SD-OCT and PRD-OCT

The SD-OCT images were obtained from all seven patients, and quantitative measurements were performed to analyze the revascularization stage.⁹ For the data of every individual patient see [Supplementary Table S2](#).

The PRD-OCT images could be obtained from all seven patients. In patient N.4 images from day 1 were

Figure 2. Cross-sectional SD-OCT B-scans, and PRD-OCT intensity and flow images of Patient N.2. Cross-sectional B-scans of Patient N.2 for SD-OCT (*left*), PRD-OCT intensity (*middle*), and PRD-OCT flow (*right*) at postoperative days 1, 5, 13, and 6 weeks and 7 months (*row-wise top-down*). In the SD-OCT images the vessel lumina are marked by *black arrows*, the thickness of the graft under the fovea is marked by a *square bracket*, and the vessel diameter is marked by a *black and white arrow*. In the PRD-OCT images *white arrows* show the presence of

flow within the graft; *black* and *white areas* indicate blood flow, *gray* represents no flow. The PRD-OCT images span over roughly half the width of the SD-OCT images as can be seen by matching the retinal structures of the SD-OCT images and the PRD-OCT intensity images. (A, B, C) One day after surgery: imbibition stage. (D, E, F) 5 days after surgery: afferent stage. (G, H, I) 13 days after surgery: efferent stage. The presence of flow is appreciated on the PRD-OCT images. (J, K, L) 6 weeks after surgery. (M, N, O) 7 months after surgery.

of very poor quality and analysis was not possible, which also was the case for the SD-OCT. Poor quality images, which made the observation of blood flow difficult, also were obtained for patient N.1 at days 15 and 31. The PRD-OCT showed flow in the graft for all seven patients. The first observation of the flow was between days 7 and 31 after surgery for the six patients who were scanned during the first postoperative period. After the first observation, all six grafts showed flow on PRD-OCT until the end of the follow-up. Patient N.7 was scanned only 1 year after surgery and showed blood flow during this visit.

Comparison of SD-OCT with PRD-OCT

We compared, in every patient, the observation of flow made with PRD-OCT to the revascularization process seen on SD-OCT. Flow was not detected by PRD-OCT at the days defined as the imbibition stage with SD-OCT in any patient. In three of six patients, flow was visible on PRD-OCT during the afferent stage as defined by SD-OCT (N.3, N.5, and N.6). For all three patients, the next follow-up visit was considered to be the start of the efferent stage on SD-OCT, as all the parameters showed that the complete graft was revascularized.

In two of six patients (N.2 and N.4) flow was seen with PRD-OCT at the same day that the start of the efferent stage was detected with SD-OCT.

In patient N.1, based on SD-OCT, the efferent stage started at day 15; however, due to suboptimal image quality, PRD-OCT data could not be obtained that day. At the next follow-up visit of this patient, day 31, flow was detected with PRD-OCT.

An example of the results for the SD-OCT and PRD-OCT measurements of patient N.2 are shown in [Figures 2](#) and [3](#). These figures show the revascularization stages, visible to the bare eye, on SD-OCT. The presence or absence of flow, detected with PRD-OCT, is shown in the same way as in [Figure 1](#). A ladder-like pattern (parallel orientation) of vessels can be clearly seen on ICGA images after a free graft transplantation.¹² This pattern is typical for the midperipheral choroid, but is atypical for the foveal area. The appearance of this ladder-like pattern on ICGA in the foveal area confirms that the angiogram shows the vessels of the transplanted graft, which is

taken from the midperiphery, and not of the underlying choroid. On PRD-OCT, this ladder-like pattern also can be appreciated, most clearly, in [Figures 3D](#) and [3F](#).

[Supplementary Clip S1](#) shows clearly, in a movie, that blood flow is visible throughout the whole graft.

Discussion

A previous study demonstrated that with SD-OCT, early perfusion and flow of an RPE-choroid graft can be imaged. Revascularization steps, as well as flow, can be inferred from structural changes on SD-OCT when a patient is scanned regularly during follow-up.⁹ We earlier reported the use of PRD-OCT for the detection of blood flow in an RPE-choroid graft.²¹ In this study both OCT methods were used side-by-side. Both SD-OCT and PRD-OCT are less invasive techniques than the currently used techniques, such as FA and ICGA,^{11,12} and, therefore, would be more applicable for frequent follow-up measurements in the evaluation of, for instance, RPE-choroid grafts.

This study was designed to confirm revascularization as suggested by SD-OCT, by flow detection with PRD-OCT. We found an overall good agreement; flow was not detected during the imbibition stage, and flow was detected for either the afferent or efferent vessel stage. Detection of flow during the afferent vessel stage with PRD-OCT probably is due to the presence of a partially revascularized graft at this stage, as described previously.⁹ The localized expansion of revascularization is much more prominently visible on FA and ICGA, but also can be visible on SD-OCT.

A drawback of identification of the revascularization by SD-OCT is that these scans need to be performed repeatedly. The first revascularization steps might be missed, because image quality of the SD-OCT scans is suboptimal if patients are not able to fixate properly, or when media opacities are present. This makes the confirmation of graft revascularization difficult: on a single late scan one cannot conclude whether the graft has slimmed down

Figure 3. Infrared and en-face PRD-OCT images of Patient N.2 Infrared images (A,C, E, G) and en face PRD-OCT images (B, D, F, H) at day 13, 6 weeks, 3 months, and 7 months postoperative. The *rectangles* depict the area where the three-dimensional PRD-OCT datasets were taken. *White circles* indicate the presence of flow, which is visualized in *black* in the choroidal vessels of the retinal pigment epithelium choroid-graft, and the *white arrows* indicate flow from retinal vessels. The *white “lines”* visible on the graft in the IR images (A, C, E, G) are folds of the graft, and have no relation to any vasculature. (A, B) 13 days after surgery. (B) *Inside the white circle the black part of the vessel indicates presence of flow in the top of the graft. The white arrow indicates flow in a retinal vessel.* (C, D) 6 weeks after surgery. (D) The PRD-OCT image shows an increased amount of blood flow in the center of the graft. The ladder-like parallel oriented pattern of the vasculature of the graft can now started to be seen. (E, F) 3 months after surgery. (D) The PRD-OCT image now outlines several complete vessels for which blood flow was detected. The ladder-like *parallel oriented pattern* of the vasculature of the graft can now more clearly be seen. (G, H) 7 months after surgery. (H) The PRD-OCT image shows ongoing revascularization which also is visible at the edges of the graft. Eye movement in the middle of the dataset created a discontinuity in the visualized blood vessel as indicated by the *white ovals*.

after the perfusion steps, or is not perfused and becoming atrophic.

The PRD-OCT might be a solution to these problems. One single scan could be performed and would be able to demonstrate flow in the graft, in just one single visit when the media are sufficiently clear, as for instance demonstrated by patient N.7.

With B-scans sections correct depth localization is achieved, and with the en face image a pseudo angiogram can be obtained.

However, the number of visualized vessels with blood flow by PRD-OCT is less than can be expected based on the number of vessels seen with SD-OCT. This suggests that our current implementation of

PRD-OCT is not able to detect all the (slow) blood flow that is assumed to exist during the start of the revascularization process. This can be attributed to the steep angle of incidence of the OCT light with retinal surface (Doppler angle), and, therefore, with the direction of the blood flow in the majority of the vessels. Consequently, the detected PRD-OCT signal is small and restricts the observation of blood flow to high flow velocities.²⁴ As stated above, the minimum detectable flow velocity ranges from 5.6 mm/s for a 70° Doppler angle to 110 mm/s for a 89° Doppler angle. Recently, it has been shown that with improved PRD-OCT scan techniques, blood flows with low velocities or with unfavorable Doppler angles can be

better observed by increasing the time interval between the compared A-scans.^{24–26} Therefore, it can be expected that the visualization of the graft revascularization with PRD-OCT will significantly improve in the future.

We conclude that PRD-OCT is able to analyze the presence of flow after RPE and choroid translocation in a single exam. Moreover, PRD-OCT confirmed the interpretation of structural and hemodynamic changes within a free RPE-choroid graft as observed previously over extended time periods with FA, ICGA, and SD-OCT.

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