Title

Post-Retinal Detachment Retinal Displacement – How Best to Detect It?

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Short Title: Post-RD retinal shift FAF comparison

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Abstract

Purpose

The reported incidence of post-retinal detachment (RD) macular displacement varies markedly (14-72%). This may in part be due to the imaging modalities used. We compared the ability of two types of fundus autofluorescence (FAF) imaging modalities to detect this phenomenon.

Methods

Prospective study of 70 eyes with macula-involving RDs. 8-weeks post-operatively, patients underwent FAF imaging with two machines: a confocal scanning laser ophthalmoscope (cSLO) and a digital fundus camera (FC). Images were graded for the presence of hyper-autofluorescent RPE ghost vessels, indicative of retinal displacement, by two masked, independent graders.

Results

87.1% of FC images were gradable versus 88.6% of cSLO images. Retinal displacement was detectable in 61.4% of FC images versus 52.8% of cSLO images. Vessel shift often appeared more autofluorescent on FC imaging, but choroidal vessels were more visible. Cohen's agreement between the imaging modalities was 0.50, rated as moderate agreement. For both imaging modalities, the inter- and intra-grader agreement was substantial, representing good test-retest reliability.

Conclusions

Detection of post-RD retinal displacement was similar between FC & cSLO FAF imaging, with only moderate agreement between both modalities.

Main Manuscript

INTRODUCTION

In recent years, there have been an increasing number of reports investigating retinal displacement following retinal detachment surgery. In 2010 Shirigami et al. described hyper-autofluorescent lines, running parallel to retinal blood vessels, apparently indicating that the retina had translocated following retinal detachment repair; they found such changes in 62.8% of a consecutive series of macular-involving retinal detachment repairs treated with vitrectomy and gas.[1] Subsequent research suggests that these hyper-autofluorescent lines, referred to as RPE ghost vessels[2] or retinal vessel printings,[3] are of functional significance due to their association with postoperative symptoms of distortion.[2] Fundus autofluorescence (FAF) imaging can be acquired with both fundus camera and confocal scanning laser ophthalmoscopy (cSLO) systems. These vary in excitation wavelengths, the nature of the barrier filter and the averaging techniques, all of which could influence the detection of excited fluorophores and thus the ability to detect retinal displacement.

Studies investigating post-operative retinal displacement have found a marked variation in the incidence, ranging from 14% - 72%.[1-7] Whilst some of the variation may be due to surgical technique or any post-operative posturing advised, it is also possible that differences in detection rates result from different imaging systems. Studies that used fundus cameras found an incidence of between 60% - 72%,[1,2,4,5] whereas studies using a cSLO system found an incidence of 14% - 41%.[3,7,8] Differences between these two imaging modalities in detecting macula pathology has previously been reported,[9,10] as has a difference in the gradability of the images due to signal to noise ratio.[10] We sought to compare both modalities with respect to their ability and reliability to detect retinal displacement, which has not previously been investigated. Due to the broader range of excitation wavelengths used by fundus camera AF, we hypothesized a higher detection rate of retinal displacement. This will be of particular importance when assessing previous and future studies investigating this phenomenon

METHODS

70 consecutive eyes of 70 patients were prospectively recruited as part of the Posturing following Retinal Detachment (PostRD) randomised controlled trial at Moorfields Eye Hospital, UK. Before participant recruitment, approval was obtained from the Moorfields Research Management Committee and National Research and Ethics Service Committee. The study complied at all times with the Declaration of Helsinki (2000) and all patients provided written informed consent before entering the study. Inclusion criteria for the trial were patients presenting with a primary, fovea-involving rhegmatogenous retinal detachment, requiring vitrectomy and gas surgery. Exclusion criteria included cases requiring intra-operative silicone oil tamponade, retinectomy or membrane peel.

Surgery and Image Acquisition

Patients underwent surgical repair with 23-gauge vitrectomy, cryopexy and gas tamponade. All patients underwent a core vitrectomy with peripheral trim without indentation. All patients underwent subretinal fluid drainage either through the largest break or a posterior retinotomy during air-fluid exchange. Perfluorocarbon liquid was not used during any of the surgeries. Patients, were randomised to either face-down or 'bubble-to-break' post-

operative posturing for the first 24 hours. Bubble-to-break posturing was variable: retinal detachments with superior breaks were postured upright, whereas those with nasal, temporal or inferior breaks were postured on the contralateral cheek. Within this subset, 32/70 (45%) were postured immediately face-down and 38/70 (55%) were postured 'bubble-to-break'. 8 weeks post-operatively, following pupillary dilatation, patients underwent FAF imaging using fundus camera and cSLO AF machines. Fundus camera AF imaging was taken using a 50-degree digital fundus camera (Topcon TRC 50IX: Topcon, Tokyo, Japan) with a 530-580nm excitation filter and 615-715nm Spaide barrier filter. Flash, gamma and gain settings were adjusted to obtain optimum image quality. cSLO AF imaging was taken using a 55-degree confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg engineering Co, Heidelberg, Germany) equipped with a 488-nm laser exciter and 500-nm barrier filter. Images were taken in high-resolution (HR) mode, with an ART of 30. Fundus camera images were always acquired first, with cSLO images acquired after at least 30 minutes later, both following a clinical trial standard operating procedure.

Image Analysis

AF images were analysed by two masked graders (EC, TH). Graders were masked to patient details and analysed both sets of anonymised images in a random order and at least two weeks apart. Alteration to image brightness and contrast was permitted to check for presence of RPE ghost vessels. Graders were asked to decide for each image whether RPE ghost vessels were present, absent or ungradable in a forced-choice manner. RPE ghost vessels were defined as hyper-autofluorescent lines running approximately parallel to retinal blood vessels and with a similar contour and calibre but separate from the blood vessel and at least 0.25 disc diameters in length (Figure 1). An image was marked as ungradable if either one of the graders felt it was ungradable. If there was a disagreement between the graders on the presence of RPE ghost vessels then a decision on whether shift was present was sought from a senior grader (EL), who remained masked and independent. Graders were also asked if choroidal vasculature was visible on the images. To assess intra-grader agreement, each grader re-graded all the images in a different order, and at least 2 weeks after their initial grading.

Statistical Analysis

Comparison of vessel shift detection by the two autofluorescent imaging modalities, inter-grader and intra-grader agreement were assessed using Cohen's κ coefficient.[11] This compares the agreement between the graders and that which you would expect by chance. If the graders are in complete agreement then κ=1. If there is no agreement other than what would be expected by chance (as defined by Pr(e)), κ=0. It should be noted that Cohen's κ coefficient is more difficult to interpret with small sample sizes. Statistical analysis was carried out using SPSS version 25.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient demographics and surgical details are shown in Table 1.

cSLO versus Fundus Camera Autofluorescence Comparison

Comparison between the cSLO and fundus camera images, for both gradability and vessel shift are shown in Table 2. 61/70 (87.1%) of fundus camera images were gradable, and shift was detectable in 43/70 (61.4%).

62/70 (88.6%) of cSLO images were gradable, and shift was detectable in 37/70 (52.8%).

There was agreement between the two imaging modalities in 50/70 (71.4%) eyes. Cohen's kappa agreement between them was 0.50, which is rated as moderate agreement.[12] This remained unchanged when excluding images that were regarded as ungradable. The graders reported consistent differences between the two imaging modalities: they found that RPE ghost vessels detected by cSLO where often less autofluorescent relative to the background fundus autofluorescence and therefore more difficult to see when compared to fundus camera AF images (Figure 1). Conversely, graders found that choroidal vasculature was more visible on fundus camera images (71.5% images graded), compared to cSLO images (7.5% images graded). This often made differentiating RPE ghost vessels from underlying choroidal vasculature challenging on fundus camera images in comparison to cSLO images (Figure 2).

Inter-Grader Grader Comparison

Inter-grader agreement is shown for the Fundus Camera AF in Table 3, and for cSLO AF in Table 4. Graders agreed on 60/70 (85.7%) of FC images and

59/70 (84.3%) cSLO images (including images assigned as ungradable). Cohen's kappa agreement between the graders was 0.72 for FC AF and 0.72 for cSLO AF. These represent substantial levels of agreement.[12]

Intra-Grader Grader Comparison

Intra-grader agreement for Grader 1 is shown for the Fundus Camera AF in Table 5, and for cSLO AF in Table 6. Cohen's kappa agreement (including images assigned as ungradable) was 0.72 for FC AF and 0.78 for cSLO AF. Cohen's kappa agreement (including images assigned as ungradable) for Grader 2 was 0.62 for FC AF and 0.61 for cSLO AF. These represent substantial levels of agreement.[12]

DISCUSSION

This is the first study to compare different fundus AF imaging modalities for detection of post-operative retinal displacement. This is of particular relevance given the recent increase in published reports investigating this phenomenon.[2-6] Post-operative retinal displacement seems to be associated with post-operative visual distortion[2] and may be reduced by post-operative posturing.[6,8]

In 2010, Shiragami et al reported the visualisation of retinal displacement following retinal detachment repair, using Topcon fundus camera AF imaging.[1] They were able to show hyper-autofluorescent lines that ran parallel to the retinal vessels, thus apparently revealing the previous anatomical position of the vessels prior to the detachment. It still remains unclear exactly what causes these hyper-autofluorescent lines. It was initially proposed that it was due to increased metabolic activity in the RPE cells that had previously not been exposed to light.[1] These vessels have been shown to persist for up to years however, when one might expect this metabolic effect to have reduced. It has therefore been suggested that the hyper-autofluorescent lines may be due to a difference in RPE fluorophores underlying retinal blood vessels, which are then only revealed after retinal detachment surgery.[13] That would also help explain the hyperfluoresent line sometimes seen at the edge of a retinal vessel in healthy retina, which has been previously put down to a refractive effect of the vessel.[14]

In the study mentioned above, Shirigami et al detected retinal shift in 62.8% of 43 eyes studied.[1] Subsequent papers that also used fundus camera

autofluorescence imaging found an incidence of post-operative retinal displacement of 60%,[15] 71.4%[4] & 72%[2] of eyes. In contrast, Dell'Omo et al used cSLO (Spectralis HRA) imaging to investigate post-operative AF changes and were able to detect retinal displacement in only 14% of macula-involving detachments.[3] In a subsequent papers by the group, also using cSLO imaging they found a slightly higher rates of displacement of 35% & 41% when using gas tamponade.[7,8] Fundus camera systems use a longer excitation wavelength (530 – 580 nm) compared to cSLO imaging (488nm) and this therefore may excite fundal fluorophores to a differing degree and this in turn may affect the rate of detection of retinal displacement. Although differing surgical techniques and post-operative posturing may well have been responsible for the variation in the reported rates of post-operative vessel shift, it is also possible that the different imaging modalities used may have contributed. It is worth noting that these studies were limited by the fact that the majority were retrospective, did not involve masked graders and did not record the proportion of ungradable images.

Our study found that fundus camera AF detected a marginally higher rate of vessel shift compared to cSLO AF (61.4% vs 52.8%). An example of a case where RPE ghosts vessels

were graded as present only in the fundus camera image is shown in Figure 3. The authors had hypothesised that the fundus camera would detect a higher rate of vessel shift compared to cSLO, given that it uses a much wider excitation wavelength (530-580 nm vs 488nm) but we did not find a significant difference. This is an important finding, given that cSLO imaging is becoming increasingly available, image acquisition is often less technically challenging compared to fundus photography and does not require a separate barrier filter. This in turn, may encourage more researchers to investigate this phenomenon.

Our findings suggest that Dell'Omo's group detected a far lower rate of RPE ghost vessels[8] compared to previous reports. This may have been due to a relatively small sample size, higher rate of PFCL use, their use of post-operative face down posturing or to the fact that they seemed to use a 35-degree FAF image for grading, which may have failed to detect more peripheral vessel shift.

We found that the proportion of images that were deemed as ungradable was similar between the two machines (12.8% vs 11.4%). This is an important observation given that it was it previously found that fundus camera AF imaging were less gradable compared to cSLO AF imaging due to signal:noise ratio when grading macular degeneration.[10] The kappa agreement between FC and cSLO images was moderate (0.5). This represents the fact that the fundus camera failed to detect 4/70 (5.7%) images with vessel shift and cSLO failed to detect 9/70 (12.8%) with shift. This may have been due to our observation that ghost vessels were more autofluorescent in fundus camera imaging, but concurrently choroidal vessels were also more visible, making grading particular images more challenging (Figure 2). This is likely due to the wider excitation wavelength used by the fundus camera. If both machines were used together, vessel shift was detectable in 64.3% of eyes, which is in keeping with previously reported rates.[1,2,4,5] It also suggests that investigation of retinal displacement may be most effective when using both FAF machines in combination.

Inter-grader and intra-grader agreement was substantial for both fundus camera and cSLO imaging (inter-grade agreement of 0.72 & 0.72; intra-grader agreement 0.72 & 0.78 respectively). For Grader 2, intra-grader agreement (0.62 for FC AF and 0.61 for cSLO AF) was lower than the inter-grader agreement (0.72 for both). This was largely down to this grader finding a higher rate of ungradable images during their second grade for both imaging systems (FC AF: 11% [1st grade] 17% [2nd grade]; cSLO AF: 10% [1st Grade] 24% [2nd grade]). The results underlie the fact Dell'Omo et al recently reported grader agreement when grading 125 cSLO FAF images with potential retinal displacement.[7] They found an agreement of 100% between the two graders, which we would regard as an unusually high rate of agreement. It may partially have been explained by the fact that they excluded poor quality images prior to the grading, which will have increased agreement. Nonetheless, we may have still expected grader agreement in our study to have been higher. This was likely due to the difficulty differentiating faint potential RPE ghost vessels from underlying choroidal vessels (Figure 4). Our findings demonstrate that there is good reproducibility for both fundus camera and cSLO image grading for vessel shift detection but by no means perfect. This is important to establish for

future trials investigating post-operative retinal vessel shift and based on these findings we would recommend using at least two graders for post-detachment FAF image assessment.

This study has a number of limitations. The first is that it is not possible to report validity of either imaging modality, as no agreed 'gold standard' for detecting vessel shift has been established yet. There are images in our series with visible outer retinal folds (and presumably accompanied retinal shift) but no obvious RPE ghost vessel visible. Therefore, these imaging modalities may not be able to detect all cases of retinal vessel shift.

CONCLUSION

Our study found that fundus camera and cSLO AF imaging were comparable for detection of post-operative retinal displacement, but with only moderate agreement. Imaging grading for both modalities had substantial agreement between graders, indicating good reproducibility.

Statements:

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Statement of Ethics: Before participant recruitment, approval was obtained from the Moorfields Research Management Committee and National Research and Ethics Service Committee. The study complied at all times with the Declaration of Helsinki (2000) and all patients provided written informed consent before entering the study.

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