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Assessment of Ischemic Index in Retinal Vascular Diseases Using Ultra Wide Field Fluorescein

Angiography: Single Versus Summarized Image

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Short Title: Retinal ischemic index

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Abstract

Background and objective: To compare a single image with a computer-generated summarized image from the ultra wide field fluorescein angiogram (UWFFA) sequence for evaluation of ischemic index (ISI).

Materials and Methods: UWFFA sequences from patients with diabetic retinopathy (DR) (n=5), branch retinal vein occlusion (BRVO) (n=5), and central retinal vein occlusion (CRVO) (n=5) were evaluated by 6 graders. A single image best illustrating retinal non-perfusion was compared to a summarized image generated by computerized superimposition of angiograms. Non-perfused, and ungradable retinal areas were outlined and the ISI between the single and summarized images was compared.

Results: The mean ISI in the single versus (vs) summarized images was 17% vs 15% in BRVO (p=0.12), 48% vs 48% in CRVO (p=0.67), and 25% vs 23% in DR (p=0.005). Inter-grader agreement of ISI in single versus summarized images was 0.43 vs 0.40 in BRVO, 0.69 vs 0.71 in CRVO, and 0.53 vs 0.34 in DR.

Conclusion: Computer-generated summarized images were similar to single images for grading ISI in BRVO and CRVO, but underestimated it in DR.

Keywords

Introduction

Diabetic retinopathy (DR) and retinal vein occlusions (RVO) are the two most common retinal vascular diseases.[1] Although the pathogenesis differs between the two, areas of non perfusion are a shared characteristic of both pathologies and vision-threatening complications such as retinal neovascularization and macular edema can develop in both. Fluorescein angiography (FA) is the gold standard for diagnosis and treatment of these diseases. With the advent of ultra-wide field fluorescein angiography (UWFFA), an image of 200 degrees of the retina can be obtained at each point in time.[2]

The development of an Automated Retinal Image Analysis (ARIA) program would likely improve screening of retinal vascular diseases as well as the objective analysis of certain features such as retinal non-perfusion.[3] Although several research studies have examined these outcomes, clinical utility with automated grading has not yet been demonstrated.[4] Our group has previously reported a manual technique to calculate an ischemic index (ISI) for the retina using UWFFA.[5, 6] Presence of retinal non-perfusion has been associated with both macular edema and neovascularization in branch retinal vein occlusion (BRVO).[5] Additionally, ISI has been reported to correlate with neovascularization in central retinal vein occlusion (CRVO) and with macular edema in DR.[6, 7] However, these retrospective studies utilize a single image from the mid venous phase of the angiographic sequence. This can be a source of error since FA is a dynamic test in which sequential images highlight different retinal features. In practice, the retinal physician commonly evaluates multiple images belonging to different phases from the same FA sequence to arrive at a diagnosis. Additionally, artifacts that appear in certain frames and not in others can be identified and ignored if multiple images are evaluated.

With these factors in mind, we hypothesized that a computerized summation and superimposition of multiple angiographic images from different phases may better highlight angiographic features such as non-perfusion compared to a single image. Furthermore, use of such a summarized image could significantly reduce the computational cost required for calculating ISI if automated image analysis were used for a full FA sequence. The development of an algorithm for the automated calculation of the ischemic index is a work in progress.[8] In the future, automated ISI calculation may become possible, but in the meantime it is important to know if ISI will need to be calculated for every phase of the angiogram or can be evaluated on one summarized image of the entire FA sequence. Accordingly, we conducted this study to evaluate whether a summarized image was equivalent to a single image from an angiographic sequence in terms of detection and measurement of retinal non-perfusion for the evaluation of the ISI.

Material and Methods

This retrospective study was performed in the Retina Division of the Jules Stein Eye Institute, University of California Los Angeles after approval from the Institutional Review Board. UWFFA images acquired between 2010 and 2011 using the Optos C200 MA scanning laser ophthalmoscope (Optos PLC, Dunfermline, UK) after standard intravenous infusion of 10% sodium fluorescein were reviewed. A total of 15 UWFFA of patients with retinal vascular diseases were included in this study. These included patients with DR (n=5), BRVO (n=5), and CRVO (n=5). Patients with vein occlusion having systemic diabetes mellitus were excluded.

For each UWFFA, each grader selected a single image out of five images in the sequence that best illustrated retinal non-perfusion. The transit eye was chosen for including in the study in

case of bilateral disease. A second image referred to as a 'summarized image' was obtained for each UWFFA by computerized summation and superimposition of five images from the angiographic sequence. Angiograms from arterial, arteriovenous, venous and late phases were all used to create the summarized image. This was based on the study hypothesis that different features captured in different phases of angiography may be better seen in a summarized image, in contrast to relying on a single image from one particular phase. The five angiographic frames were superimposed using the RERBEE image registration algorithm,[9] and a composite summarized image was created by calculating the pixel-wise mean-intensity of the sequence frames. Figure 1 illustrates a single image and its corresponding summarized image.

Six independent graders composed of 5 retina fellows and 1 retina faculty graded the single image and the summarized image for each UWFFA. The graders were instructed to outline total retinal area, non-perfused retinal area, and area that was ungradable due to artifacts using annotations on Adobe Photoshop software. Non-perfused area was defined as an area of the retinal angiogram lacking vessels altogether but flanked by neighboring filled vessels, and areas lacking texture and showing no change in texture in early versus late frames. Areas of the retinal angiogram that were ambiguous and could not be classified as non-perfused versus non-imaged/out-of-focus with certainty, because of peripheral nature of such an area and because of curved nature of peripheral retina, was called ungradable. Figure 2 illustrates the grading technique. The number of pixels occupied by the outlined areas was determined using the same software. These data were then translated into percentage of non-perfused retinal area (ISI) and percentage of ungradable retinal area, and the values were compared between single and summarized images. Additionally, inter-grader agreement was calculated using intraclass correlation coefficient (ICC) and was also compared between single and summarized images.

Results

All six graders completed grading of single and summarized image for each of the 15 UWFFA. The mean total retinal area (in pixels) was significantly greater for single images versus summarized images in BRVO (8326505 versus 7760461, p=0.0006), CRVO (8620926 versus 8127615, p=0.0004), and DR (8631410 versus 8336582 p=0.002). The percentage of areas graded as nonperfused retinal area and ungradable retinal area for each disease are compared in Table 1. The nonperfused retinal area in BRVO and CRVO, and the ungradable retinal area in all three diseases were statistically similar in single versus summarized images. The nonperfused retinal area was statistically lower in the summarized image than in the single image for DR.

The inter-grader agreement for nonperfused and ungradable retinal areas in single and summarized images are shown in Table 2. For nonperfused retinal area, the single image had a marginally greater inter-grader agreement compared to the summarized image for all three diseases. For ungradable retinal area, the summarized image had a greater intergrader-agreement than single image in CRVO, and the single image had a greater intergrader-agreement than summarized image in DR, whereas both single and summarized image had a very poor inter-grader agreement (<0.001) for BRVO.

Discussion

Visualization of retinal non-perfusion in the periphery has been greatly facilitated by UWFFA.[5, 6] The ischemic index, which is a measure of retinal non-perfusion on UWFFA, has been reported to correlate well with the extent of neovascularization in CRVO, and with macular

edema in DR.[6, 7] One of the rationales for using a summarized image in our study was the hypothesis that angiographic features highlighted in different FA phases may be better delineated in the form of a summarized image. While evaluation by a clinician of the individual images from an angiographic sequence may be the best option to highlight specific features, it can be costly and time consuming. Moreover, there is subjectivity involved in evaluation of FA images, mental superimposition of the different images of the sequence may be erroneous, and interpretation of angiography results may vary. Automated analysis may offer a more objective and consistent approach in this regard. For automated analysis, a summarized image seems more practical as opposed to analysis of multiple single images because automated analysis of multiple single images adds to the computing cost, specifically increasing the time and computer memory required for the program to run through the analysis algorithm several times for each image. Analyzing a summarized image instead of multiple single images, on the other hand, may save time and computer resources.

For grading ISI, we found single and summarized images to be equivalent for RVO but not for DR. We speculate that during superimposition of separate angiographic images from different phases, some definition may be lost. Such loss of definition may be less significant in RVO where perfused areas occupy a large confluent area, making grading less controversial. Conversely with DR, the non-perfused areas are usually small with a patchy distribution. The computerized summarizing process may result in some of the smaller non-perfused areas of DR to be masked due to image averaging, while the larger non-perfused areas of RVO may escape such a phenomenon. Alternatively, the single image could potentially overestimate the non-perfused area by relying on a single frame of the sequence making the summarized image more

accurate in this regard. A single image may also miss retinal non-perfusion because of difficulty to judge rate of perfusion without access to successive angiographic sequence.

Inter-grader agreement of singles images in patients with CRVO has been reported to be lower for grading macular ischemia compared to macular edema.[10] Retinal non-perfusion appears as an area with loss of fine detail with hypofluorescence flanked by retinal vessels. Retinal edema, on the other hand, manifests as leakage and hyperfluorescence. Consequently, detection and outlining of non-perfused areas may be challenging and more subjective than that of retinal edema. In our study, single and summarized images had similar inter-grader agreement for retinal non-perfusion in BRVO and CRVO, but slightly better agreement for the single image in DR (Table 2). This further supports the notion that the summarized image may be equivalent to a single image and therefore appropriate for an automated image analysis protocol for RVO. It will be important to compare human grading versus computerized automated grading in the future.[8]

It is notable that although the absolute total retinal area was significantly greater for single images than summarized images, the percentage of nonperfused retinal area was similar, especially for RVO. It seems that either the summarized image underestimated or the single image overestimated the total retinal area and the non-perfused area proportionally, so that the percentage remained similar in single and summarized image.

It is important to note that UWFFA images are subject to geometric distortion, due to the process of projecting a three dimensional retina onto a two dimensional image plane. This may lead to distortion of the shape and area of ischemic retina in captured images compared to their true configuration. We speculate that the averaging achieved in a summarized image and the resulting dilution of distortion may produce a more consistent representation of the retina than a

single image in which the distortion may vary. While it is not yet possible to measure ischemic regions directly on the retina, related research in the re-projection of UWFFA images that preserve properties such as angles and areas may offer further support to the results presented in this paper.

Limitations of this study include lack of validation of the summarization technique used, small sample size, and lack of control images. Even so, to the authors' knowledge, this is the first study investigating the use of a summarized image obtained by computerized superimposition of multiple angiographic images from different phases to measure retinal non-perfusion. In the future a summarized image may provide a faster and easier alternative to grading all sequence of images provided by the angiography, especially with respect to developing an automated algorithm for calculating an ischemic index in RVO. Further studies are needed for DR grading, and also for comparing human versus computer grading of non-perfusion.

Declaration of Interest

The authors report no conflicts of interest.

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