

Fluorescein Angiography in Uveitis: Still a Gold Standard

Angiografia Fluoresceínica na Uveíte: Ainda um *Gold Standard*

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ABSTRACT

INTRODUCTION: Despite advances in imaging, color fundus photography remains widely used in the assessment of posterior uveitis, although it provides only structural information. In contrast, fluorescein angiography (FA) allows dynamic visualization of retinal vascular involvement. This study aimed to characterize the use of FA in clinical practice among Portuguese ophthalmologists with experience in ocular inflammation and to assess their ability to predict angiographic abnormalities based solely on fundus photographs.

METHODS: A questionnaire with five questions regarding clinical indications for FA in uveitis was sent to Portuguese ophthalmologists experienced in ocular inflammation. A subgroup of these participants also completed a second component in which they were asked to analyse 17 consecutive fundus photographs from patients with uveitis and predict the presence of angiographic abnormalities.

RESULTS: Ten responses were obtained regarding FA use in clinical practice. Sixty percent of participants reported that FA is routinely requested at the time of diagnosis in cases of suspected posterior segment involvement. Seventy percent considered segmental or diffuse vascular sheathing to be the fundusoscopic sign best characterized with FA. Eighty percent used FA as a follow-up tool to monitor clinical response in retinal vasculitis, and 60% reported a preferred follow-up interval of 3 to 6 months. Eight participants completed the image-based component. Full agreement among all ophthalmologists regarding the prediction of FA abnormalities was achieved in only 4 of the 17 cases. The mean prediction accuracy was 64.71%. Focal retinal or choroidal lesions were the easiest to predict, whereas retinal vasculitis was more difficult, with only 32.5% correctly predicting vascular leakage. Peripheral lesions were the most challenging, with 0% correct predictions in two cases.

CONCLUSION: FA is considered a valuable diagnostic tool by most ophthalmologists surveyed, both for baseline assessment of posterior uveitis and for follow-up in retinal vasculitis. However, a considerable percentage of clinicians were unable to predict angiographic abnormalities based solely on fundus photographs. These results suggest that FA remains essential in the diagnostic workup of uveitis, as retinal or choroidal changes may go undetected even after careful fundus examination.

KEYWORDS: Fluorescein Angiography; Uveitis/diagnostic imaging.

RESUMO

INTRODUÇÃO: Apesar do desenvolvimento de novas técnicas de imagem, como a tomografia de coerência ótica (OCT) e a angiografia por OCT (OCTA), a angiografia fluoresceínica (AF) continua a ser um exame de referência na avaliação da uveíte, permitindo detetar extravasamento vascular, áreas de isquemia e vasculite retiniana. Este estudo teve como objetivo caracterizar a utilização da AF na prática clínica de oftalmologistas portugueses com experiência em inflamação ocular e avaliar a capacidade destes em prever alterações angiográficas com base exclusivamente em retinografias a cores.

MÉTODOS: Foi realizado um estudo observacional composto por duas partes. A primeira consistiu num questionário constituído por cinco perguntas sobre as indicações clínicas para realização de AF em doentes com uveíte. Na segunda parte, um subgrupo de participantes analisou 17 retinografias consecutivas de doentes com uveíte, classificando a probabilidade de alterações na AF e seleccionando os achados angiográficos que antecipavam encontrar.

RESULTADOS: Foram obtidas dez respostas ao questionário clínico. Sessenta por cento dos oftalmologistas realizam AF no diagnóstico quando existe suspeita de envolvimento do segmento posterior e 80% recorrem à AF no seguimento da vasculite retiniana. A maioria (60%) considerou um intervalo de 3 a 6 meses adequado entre exames de seguimento e 70% identificou o embainhamento vascular como o achado fundoscópico mais bem caracterizado pela AF. Na análise das imagens, oito participantes completaram a avaliação de 17 casos. A concordância total entre observadores verificou-se apenas em 23,5% das imagens. A precisão média das previsões foi de 64,71%. As lesões focais foram as mais facilmente reconhecidas, enquanto a vasculite retiniana foi subestimada (32,5% de respostas corretas) e as lesões periféricas foram as mais difíceis de antecipar (0% de acerto em dois casos).

CONCLUSÃO: A AF mantém um papel central na abordagem diagnóstica e monitorização da uveíte, sendo amplamente utilizada por especialistas portugueses em inflamação ocular. Este estudo demonstra que, apesar da experiência clínica dos participantes, a avaliação baseada apenas em retinografias não permite identificar de forma fiável alterações angiográficas, reforçando a importância da AF na deteção de inflamação subclínica e na orientação terapêutica.

PALAVRAS-CHAVE: Angiografia Fluoresceínica; Uveíte/diagnóstico por imagem.

INTRODUCTION

Despite advances in imaging, color fundus photography remains widely used in the initial assessment of posterior uveitis, although it provides only static structural information. In contrast, fluorescein angiography (FA) offers dynamic visualization of retinal vascular leakage and non-perfusion, allowing the detection of inflammatory changes that may not be clinically evident on fundus examination.^{1,2} While it is clinically recognized that fundus photographs may underestimate vascular activity, this limitation is not usually objectively measured against FA findings.

This study aimed to characterize how Portuguese ophthalmologists experienced in ocular inflammation utilize FA in routine clinical practice and to evaluate their ability to predict angiographic abnormalities based solely on color fundus photographs.

METHODS

STUDY DESIGN AND PARTICIPANTS

This was a cross-sectional observational study conducted among Portuguese ophthalmologists with experi-

ence in ocular inflammation. Ten specialists were invited to complete a two-part questionnaire addressing their use of FA in uveitis diagnosis and management. Participation was voluntary and anonymous.

QUESTIONNAIRE ON FA USE

The first part of the study consisted of five multiple-choice questions concerning the practical use of FA in patients with uveitis. The questionnaire explored: indications for requesting FA at diagnosis; use of FA for follow-up evaluation; preferred intervals between examinations; fundoscopic signs in anterior uveitis that prompt FA; and clinical situations where FA is considered less safe.

The full set of questions is provided in [Appendix 1](#).

EVALUATION OF FUNDUS PHOTOGRAPHS

Eight of the ten participants completed the second part of the study, which consisted of evaluating a series of color fundus photographs. Seventeen consecutive images from patients with uveitis followed at the Ocular Inflammation Unit of the Ophthalmology Department of Hospital Egas Moniz and Hospital CUF Tejo were selected, ensuring that only one eye per patient was included. All images were obtained after

pharmacological mydriasis and met predefined quality criteria for adequate visualization of both the posterior pole and peripheral retina. To ensure methodological consistency, the images were presented to all participants in the same order.

Participants were informed that the images represented fundus photographs of different uveitis cases. For each image, they were asked to indicate, on a five-point scale (1=very unlikely; 5=very likely), how probable it was that fluorescein angiography would reveal any abnormalities. When the assigned score was equal to or greater than 2, they were further asked to specify which angiographic alterations they expected to find. The possible options included late optic disc leakage, late macular leakage, diffuse or segmental retinal vasculitis, focal retinal or choroidal lesions, capillary dropout (ischemia), and retinal or choroidal neovascularization.

The reference standard for each image corresponded to the actual fluorescein angiography findings, which had been previously analysed and validated by two uveitis specialists.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the data. Responses from the questionnaire were expressed as the percentage of participants selecting each option. For the image-based assessment, accuracy was calculated as the proportion of correct predictions for each photograph, and overall mean accuracy was determined across all images. Inter-rater agreement for the binary prediction of the presence or absence of angiographic abnormalities was assessed using Fleiss' kappa (κ).

RESULTS

QUESTIONNAIRE ON FA USE

Ten ophthalmologists completed the first section of the questionnaire. Most participants reported that they usually request FA at diagnosis whenever posterior segment involvement is suspected, while a smaller proportion indicated they reserve it for more specific findings such as vasculitis or vascular leakage suspicion.

During follow-up, the majority of respondents stated that FA is mainly used to monitor clinical response in cases of retinal vasculitis, with only a few indicating other purposes such as evaluation of focal inflammatory or ischemic lesions. In terms of timing, most participants preferred to repeat FA every three to six months, whereas some opted for longer intervals of six to twelve months.

In cases of anterior uveitis, segmental or diffuse vascular sheathing was the fundoscopic sign that most frequent-

ly prompted the use of FA, followed by macular edema or focal inflammatory lesions. When asked about safety, the large majority considered the examination less safe in patients with a known allergy to fluorescein dye.

These findings are summarized in Table 1.

EVALUATION OF FUNDUS PHOTOGRAPH PREDICTIONS

Eight specialists evaluated 17 fundus photographs. The mean overall prediction accuracy was 64.71%. Complete agreement among all participants occurred in four of the seventeen images (23.5%). Inter-rater agreement for predicting the presence or absence of FA abnormalities was low, with Fleiss' $\kappa = 0.218$ (borderline slight-fair agreement),³ reflecting limited consistency among observers when FA was not available.

When evaluating the ability to detect angiographic abnormalities, participants showed high sensitivity (83.0%), correctly predicting the presence of FA abnormalities in most pathological cases. However, specificity was low (33.3%), indicating difficulty in correctly predicting normal angiograms and excluding posterior segment inflammation based solely on fundus photographs.

Although many participants anticipated that FA would reveal abnormalities, the specific angiographic pattern was often misclassified. Prediction performance varied by lesion type. Optic disc leakage and macular leakage were the most difficult findings to predict accurately. Retinal vasculitis (segmental or diffuse) was also frequently misclassified. Focal retinal or choroidal lesions were recognized more consistently, and ischemia showed the highest correct prediction rate (Table 2).

Table 2. Prediction Accuracy by Angiographic Finding.

Angiographic finding	Accuracy (%)
Optic disc leakage	0.0%
Macular leakage	12.5%
Retinal vasculitis (segmental/diffuse)	29.2%
Focal retinal/choroidal lesions	55.0%
Ischemia/Capillary dropout	87.5%

A representative example is shown in Fig. 1.

DISCUSSION

In this study, we evaluated the use of FA in the management of uveitis among Portuguese ophthalmologists

Table 1. Summary of Responses on the Use of Fluorescein Angiography in Uveitis.

Domain	Most Frequent Response	% of Participants
Indications for FA at diagnosis	Suspicion of posterior segment involvement	60%
FA for follow-up	To assess clinical response in retinal vasculitis	80%
Preferred follow-up interval	Every 3–6 months	60%
Fundoscopic sign prompting FA (anterior uveitis)	Segmental or diffuse vascular sheathing	70%
Situations where FA is least safe	Known allergy to fluorescein	80%

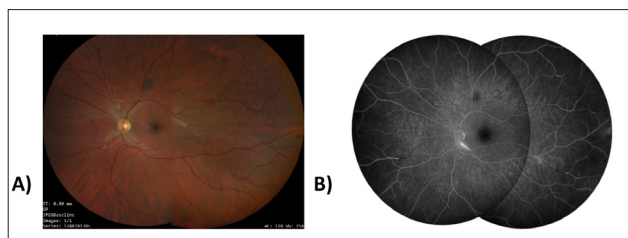


Figure 1. Example of a misclassified case. (A) Fundus photograph. (B) Corresponding fluorescein angiography showing segmental retinal vasculitis.

with experience in ocular inflammation and assessed their ability to predict angiographic abnormalities from fundus photographs. The results highlight the central role of FA in clinical practice and demonstrate the limitations of relying solely on color fundus imaging for detecting posterior segment vascular pathology.

The first part of the study confirmed that FA remains a widely used diagnostic tool, particularly in suspected posterior segment involvement. Most participants (60%) reported performing FA at diagnosis in such cases, and 80% used FA during follow-up to monitor retinal vasculitis. These findings are consistent with current clinical practice, where FA is still considered the reference method for detecting retinal vascular leakage, capillary nonperfusion and subclinical inflammation not visible on ophthalmoscopy or optical coherence tomography (OCT).⁴

In the image-based analysis, even experienced ophthalmologists demonstrated difficulty accurately predicting FA findings based solely on fundus photographs. Although the overall prediction accuracy was 64.71%, diagnostic performance varied markedly by lesion type. Ischemia was the most accurately predicted angiographic finding (87.5%), likely due to structural clues visible on fundus photographs. In contrast, optic disc leakage (0.0%) and macular leakage (12.5%) were rarely predicted correctly, and retinal vasculitis (segmental or diffuse) was correctly identified in only 29.2% of cases. Despite this, participants showed high sensitivity (83.0%) in detecting that FA would be abnormal, but specificity was low (33.3%), indicating difficulty in distinguishing normal from abnormal eyes based only on fundus examination. Inter-observer agreement was low (Fleiss' $\kappa = 0.218$), reflecting variability in clinical interpretation when FA is not available. These findings reinforce previous evidence showing that FA frequently reveals subclinical inflammatory activity.⁵

Several factors may explain the limited predictive accuracy observed. First, color fundus imaging lacks the dynamic information needed to detect vascular leakage, particularly in the retinal periphery. Second, inflammatory changes may precede structural alterations, making FA the only imaging modality capable of detecting early vasculitic activity.⁶ Third, individual variability in clinical interpretation may contribute to inconsistent assessments, as reflected by the low inter-rater agreement in our study. Together, these findings underscore the diagnostic uncertainty that exists when FA is omitted.

Given these results, FA should be considered a fun-

damental imaging tool in the evaluation of uveitis. The high sensitivity in detecting that angiographic abnormalities were likely (83.0%), combined with the low specificity (33.3%) and poor inter-observer agreement ($\kappa = 0.218$), indicates that fundus examination alone is insufficient to reliably exclude posterior segment involvement. Therefore, FA should be performed at baseline in all cases with suspected posterior uveitis, as failure to do so may lead to underestimation of inflammatory activity. Additionally, the frequent underprediction of vascular leakage and retinal vasculitis—particularly in images without overt fundoscopic signs—supports the use of repeat FA during follow-up when monitoring treatment response or when vascular inflammation remains clinically uncertain. Reliance solely on fundus imaging risks missing ongoing activity and may result in delayed therapeutic escalation.

Although the findings are relevant, some limitations must be considered. The sample size was relatively small, particularly in the image-based assessment ($n = 8$) and participants did not have access to clinical context or multimodal imaging, which could have improved prediction accuracy. Nonetheless, these conditions allowed us to isolate the true diagnostic value of fundus photographs and quantify the contribution of FA in uveitis evaluation.

CONCLUSION

Fluorescein angiography remains indispensable in the evaluation of posterior uveitis and retinal vasculitis. While color fundus photographs can suggest inflammatory activity, they do not provide sufficient information to characterize vascular involvement. In this study, clinicians frequently suspected angiographic abnormalities but showed limited diagnostic agreement (Fleiss' $\kappa = 0.218$) and low specificity when FA was not available, highlighting the risk of underestimating inflammatory activity based solely on fundus evaluation. Systematic use of FA at diagnosis and during follow-up, particularly in suspected retinal vasculitis or vascular leakage, remains essential for accurate disease monitoring and informed treatment decisions.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

JR: Conceptualization, formal analysis, data collection, writing of the original draft, review and editing.

MG: Conceptualization, critical review and editing.

NC: Manuscript review.

AR and MTC: Data collection.

All authors have read and approved the manuscript.

JR: Conceitualização, análise formal, recolha de dados, redação do rascunho original, revisão e edição

MG: Conceitualização, revisão crítica e edição.

NC: Revisão do manuscrito.

AR e MTC: Recolha de dados.

Todos os autores leram e aprovaram o manuscrito.

RESPONSABILIDADES ÉTICAS

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

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Appendix 1. Questionnaire on the Use of Fluorescein Angiography in Uveitis**Question 1.**

In the context of uveitis, in which situations do you usually request fluorescein angiography (FA) at the time of diagnosis?

- In all patients diagnosed with uveitis, regardless of location.
- Whenever there is suspicion of posterior segment involvement.
- Whenever there is suspicion of papillary or macular edema, or vascular leakage.
- Whenever fundoscopic signs suggest retinal vasculitis.
- Whenever there is suspicion of retinal ischemia or neovascularization.
- Whenever there is suspicion of choroidal neovascularization.

Question 2.

In the context of uveitis, for what purposes do you most frequently request FA during follow-up?

- To assess clinical response in cases with papillary and/or macular edema.
- To assess clinical response in the presence of segmental or diffuse retinal vasculitis.
- To assess clinical response in the presence of focal inflammatory retinal or choroidal lesions.
- To assess clinical response in cases of retinal ischemia or neovascularization.
- To assess clinical response in cases of choroidal neovascularization.

Question 3.

When angiographic abnormalities are documented at diagnosis, how frequently do you usually repeat FA during follow-up?

- Every 0–3 months.
- Every 3–6 months.
- Every 6–12 months.
- Annually.

Question 4.

In a patient with anterior uveitis, which fundoscopic findings most frequently lead you to request FA?

- Optic disc edema.
- Macular edema.
- Vitritis.
- Segmental or diffuse vascular sheathing.
- Retinal hemorrhages.
- Peripheral snowballs or snowbanking.
- Suspected retinal neovascularization.
- Suspected choroidal neovascularization.
- Retinitis or chorioretinitis lesions.
- Lesions suggestive of chorioiditis.
- Cotton-wool spots.

Question 5.

In which patients do you consider FA less safe to perform?

- Children.
- Pregnant women.
- Poorly cooperative patients.
- Patients with renal insufficiency.
- Patients with a known allergy to fluorescein dye.