Application of Creative Quantitative Measurement of Iris Angiography in Diabetic Retinopathy

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Research Article

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Abstract

Background: To explore the application of a creative quantitative measurement of iris angiography (IA) in diabetic retinopathy (DR).

Methods: This was a single-center cross-sectional study. From May 2016 to December 2019, 30 consecutive patients (60 eyes) with severe non-proliferative diabetic retinopathy (NPDR) and 30 consecutive patients (60 eyes) with proliferative diabetic retinopathy (PDR) who underwent IA in Tianjin Medical University Eye Hospital were enrolled prospectively in the study. All of the patients underwent ophthalmologic examination including visual acuity, intraocular pressure, slit-lamp microscopy, slit-lamp anterior lens, ultra-wide-field fundus photography and IA. IA included iris fluorescein angiography (IFA) and iris indocyanine green angiography (IICGA). The onset time of iris vascular leakage should be recorded and the circumference range of pupil margin fluorescein leakage was measured by self-developed software. Independent sample t-test and chi-square test were used to compare and analyze the difference of the onset time and range of iris vascular leakage between severe NPDR and PDR groups.

Results: IFA showed that the onset time of iris vascular leakage was 30.38±6.40s in severe NPDR group and 26.50±5.41s in PDR group. The difference between two groups was statistically significant (p=0.006). The range of iris vascular leakage was 49.09±59.27 degrees in severe NPDR group and 137.71±95.53 degrees in PDR group. There was significant statistically difference between two groups (p=0.032). No neovascularization of the iris (NVI) was found in all patients with PDR by slit-lamp microscope examination, while NVI was detected in 8 eyes by IFA and IICGA examination.

Conclusions: The creative quantitative measurement of IA can evaluate the severity of diabetic iridopathy (DI), monitor the progress of DR, and detect NVI invisible to the naked eye as soon as possible, so as to provide a basis for the formulation of personalized treatment for patients with DR.

Background

Diabetic ocular microangiopathy mainly includes diabetic iridopathy (DI) and diabetic retinopathy (DR) [1]. Iris angiography (IA), which primarily includes iris fluorescein angiography (IFA) and iris indocyanine green angiography (IICGA), has been used for evaluation of DI [2]. However, there is no quantitative evaluation of the severity of DI at present. To assess the advantage and sensitivity of quantitative measurement of IA in DR evaluation, a group of patients with DR underwent IA and the results are reported as follows.

Methods

Study design and participants

This is a single-center cross-sectional study. This study was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (2016KY-04). Informed consent was obtained from parents and

participants 18 years or older.

From May 2016 to December 2019, 60 patients (120 eyes) with DR who underwent IA in Tianjin Medical University Eye Hospital were recruited in the study. There were 25 cases (50 eyes) of males and 35 cases (70 eyes) of females with an average age of 53.5±10.7 years (range, 37–75 years). All of the patients underwent standard ophthalmologic examination including visual acuity, intraocular pressure, slit-lamp microscopy, slit-lamp anterior lens, ultra-wide-field fundus photography and so on. They were all diagnosed as severe non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). Enrollment criteria include: (1) confirmed diagnose of type 1 or type 2 diabetes; and (2) evidence that fundus examinations of patients with severe NPDR conformed to Early Treatment of Diabetic Retinopathy Study (ETDRS) classification; those of patients with PDR showed a small amount of subvitreous hemorrhage / preretinal hemorrhage or retinal neovascularization. Exclusion criteria include: (1) combination with retinal vein occlusion, neovascular glaucoma (NVG); (2) significant dioptric media opacities (such as severe keratopathy, cataract and vitreous hemorrhage), which interfered with IA imaging; and (3) any histories of retinal photocoagulation, intravitreous anti-vascular endothelial growth factor (VEGF) injections, vitrectomy or other ocular surgeries.

IA

All patients underwent detailed slit lamp microscope examination to determine whether there were small striped red vessels (neovascularization of the iris (NVI)) on the iris surface or pupil margin. IFA and IICGA were performed using German Heidelberg confocal laser scanning fundus angiography instrument (Spectralis HRA). None of patients had fluorescein sodium allergy and no pupil dilatation were needed during the examination. The mixture of 10% fluorescein sodium (3ml) and aseptic injection (3ml) dissolving indocyanine green (25mg) was quickly injected through cubital vein within 5 seconds. Firstly, IFA and IICGA were obtained with lens focusing on the iris. Abnormal iris vessels enhancement and the onset time of fluorescein leakage within the first one minute were recorded. Then, IFA and IICGA examinations were performed again within 4–10 minutes for a comparison between earlier and later stage of iris fluorescein leakage.

Quantitative analysis of iris angiography (Patent Application Number: 202010476895.1)

Once the imaging of IA was derived, the circumference range of pupil margin fluorescein leakage was measured by the self-developed measurement software. The protocol was as follows: (1) Mark the center point. Click on the center of the pupil to determine the center point (Fig. 1). (2) Mark the range of leakage lesions. Set up the starting and ending points of all lesions in selected area where the lesion was. That was obtained by clicking on each end of the uninterrupted fluorescein leakage lesion once. A corresponding angle were generated after the starting and ending points were selected. Different colors were applied on multiple leakage lesions automatically through the software (Fig. 2). (3) Record the total circumference of all the leakage lesions. After the marking of lesions range, click the calculation function of the software to automatically calculate the total angles of the pupil margin fluorescein leakage lesions

(Fig. 3). The leakage ranges of all patients were repeatedly marked and measured three times, and then averaged.

Statistical analysis

All statistical analyses were done applying SPSS software version 22.0. All the measurement data were expressed as mean ± standard deviation (± s), and the onset time and range of iris vascular leakage in two groups were analyzed by independent sample t-test. The rates of count data were analyzed by chi-square test. Differences were considered statistically significant at $p < 0.05$.

Results

The onset time and range of iris vascular leakage on the exam eye were selected for statistical analysis of in all patients. The results of IFA demonstrated that the onset time of iris vascular leakage in patients with severe NPDR was 30.38 ± 6.40s, and that in patients with PDR was 26.50 ± 5.41s. The difference between two groups was statistically significant ($p = 0.006$). The range of iris vascular leakage in patients with severe NPDR was 49.09±59.27 degrees, and that in patients with PDR was 137.71±95.53 degrees. There was significant difference between two groups ($p = 0.032$) (Table 1).

Table 1
IA findings of severe NPDR and PDR patients

Group	Number of leakage cases	Number of no leakage cases	Onset time of leakage (s, mean ± SD)	Range of leakage(degree, mean ± SD)
severe NPDR	26	4	30.38 ± 6.40	49.09 ± 59.27
PDR	30	0	26.50 ± 5.41	137.71 ± 95.53
p			0.006	0.032
SD, standard deviation				

None of NVI was observed in all patients examined by slit lamp microscope, while there were 8 eyes diagnosed as NVI using IFA and IICGA examination, there was significant difference between these two examinations ($p < 0.001$). IFA findings revealed that NVI presented as abnormal neovascularization with early leakage and the vascular morphology was quickly blurred due to obvious leakage. While during IICGA, NVI presented as abnormal neovascularization with fuzzy outline at the beginning but clear vascular morphology presented gradually (Fig. 4,5).

Discussion

The formation of NVI is a risk factor for the occurrence of NVG [3–5]. With the progression of DR, retinal ischemia is gradually aggravated, which leads to NVI and even NVG [6, 7]. Early detection of NVI can

predict the occurrence of NVG. There is a significant correlation between DI and severity of DR. The severity of DI can be evaluated by IA examination, especially when a clear fundus image can not be obtained due to dioptric media opacities. The IA imaging can provide a crucial basis for determining of the stage of DR [8], identify high-risk DR patients and offer personalized treatment for the patients with DR. Since the iris vessels in the early stage of DR patients are mostly in the deep layer of iris stoma, and with more iris pigments in Chinese population, it is difficult to detect the lesion at the early stage with slit lamp microscope. Whereas IA can detect early abnormal neovascularization [9], providing a method of evaluating whether DR patients have NVI.

Numerous researches [10, 11] have found that IFA is easier to find early NVI than IICGA. Through the different characteristics of fluorescein leakage in IFA, we can distinguish iris capillary leakage from NVI. Iris capillary leakage on IFA presented as mild fluorescein leakage with short duration, while NVI presented as moderate or severe leakage with longer duration. Animal experiments found that there was no leakage of iris vessels in IICGA, which could better display the details of iris vessels. IICGA has better diagnostic and application value in iris angiography than IFA [12]. The results of this investigation also suggested that IFA showed NVI filled and leaked rapidly, but in the middle and late stages, with the increase of leakage, IFA could not present the morphology of NVI well. Also, it was difficult to distinguish NVI from pathological iris capillary leakage. On the contrary, IICGA was showing limited NVI leakage, the morphology of abnormal NVI progression was better be observed in middle and late stage, which could well distinguish NVI from iris capillaries. Therefore, we think that IFA combined with IICGA can effectively diagnose NVI and help to distinguish it from iris capillaries or pathological iris capillary leakage.

In order to evaluate the severity of DI in an even better fashion, this research creatively used the self-developed measurement software to accurately measure the circumference range of pupil margin fluorescein leakage. The findings documented that the onset time of iris vascular leakage in PDR patients was significantly earlier than that in severe NPDR patients, and the range of iris vascular leakage in PDR patients was also significantly larger than that in severe NPDR patients, indicating that the more serious the condition of DR, the more obvious the leakage of iris. Among them, NVI was found in 8 patients with PDR who received IA imaging, while in none of patients with severe NPDR. The results demonstrated that with the development of DR, the severity of the retinal ischemia and hypoxia gradually increased and a large amount of neovascular growth factor was released, especially VEGF. The VEGF released into the vitreous cavity gradually spread to the anterior chamber, which eventually led to the formation of NVI. Thereby, the creative quantitative measurement method of IA provides a reference for the application of quantitative evaluation of DI in ischemic ophthalmopathy.

Investigations have found that VEGF is a key factor in the occurrence and development of NVG. Anti-VEGF drugs are an important auxiliary means for the prevention and treatment of NVG, and vitreous injection of anti-VEGF drugs in the short term is a significant strategy for the treatment of NVG [13–16]. In this study, there were 8 PDR patients with NVI. We timely explained the risk of NVG and treatment recommendations to the patients. For the patients with clear dioptric medium, we first injected anti-VEGF drugs into the vitreous cavity, and then completed panretinal photocoagulation (PRP) 2 weeks later. The

spot effect was grade 3, and the spot interval was half a spot diameter. For the patients with vitreous hemorrhage, we completed the vitrectomy as soon as possible. PRP was performed during the operation and the spot should be dense enough. Anti-VEGF drugs were given at the end of the operation. Through the above treatment, the NVI of all patients disappeared, the condition was effectively controlled, and did not progress to NVG.

At the same time, this study also found that iris leakage in PDR patients with NVI was significantly more severe than that without NVI. Because the number of PDR patients with NVI was relatively small, we did not statistically analyze the data of the two subgroups and could not draw a more reliable conclusion. In the follow-up study, we will continue to accumulate cases and compare the iris leakage between PDR patients with NVI and without NVI, hoping to obtain reliable indicators for early warning of the occurrence of NVG.

To sum up, quantitative measurement of IA can better evaluate the severity of ischemia in patients with DR and early identify high-risk DR patients prone to NVG, so as to provide a reference basis for personalized treatment of DR.

Abbreviations

DI: diabetic iridopathy; DR: diabetic retinopathy; IA: iris angiography; IFA: iris fluorescein angiography; IICGA: iris indocyanine green angiography; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; NVG: neovascular glaucoma; VEGF: vascular endothelial growth factor; NVI: neovascularization of the iris; PRP: panretinal photocoagulation

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (2016KY-04). All procedures were performed in accordance with relevant guidelines. Informed consent was obtained from parents and participants 18 years or older. There was no risk or hazardous procedures putting the participants at harm.

Consent for publication

Consent for publication was obtained from the participants.

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZQ and AWT participated in data collection/ analysis and drafted the manuscript. HJD and ZLL conceived the idea of the study, designed the study and revised the manuscript critically. All authors read and approved the final manuscript.

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Figures

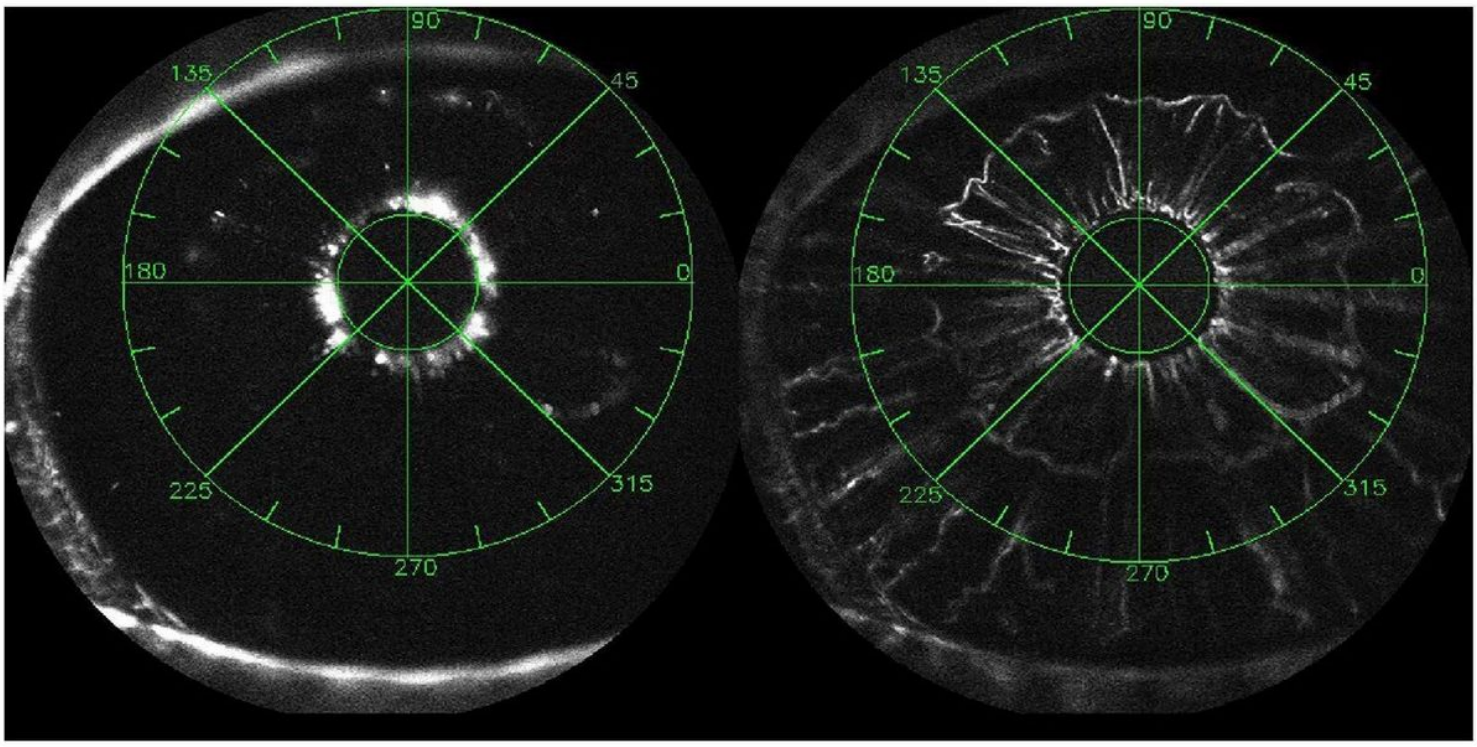

Figure 1

Marking of center point

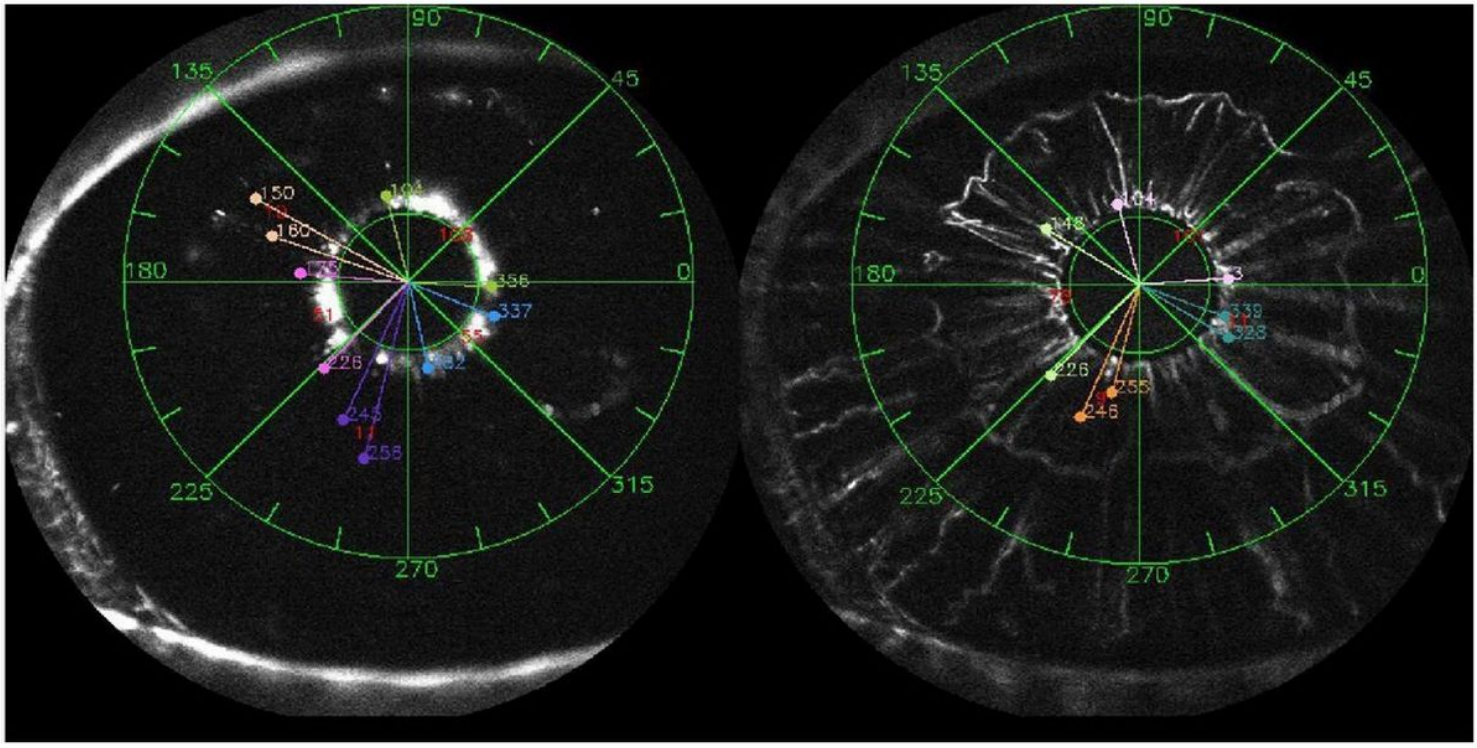

Figure 2

Marking of lesions range

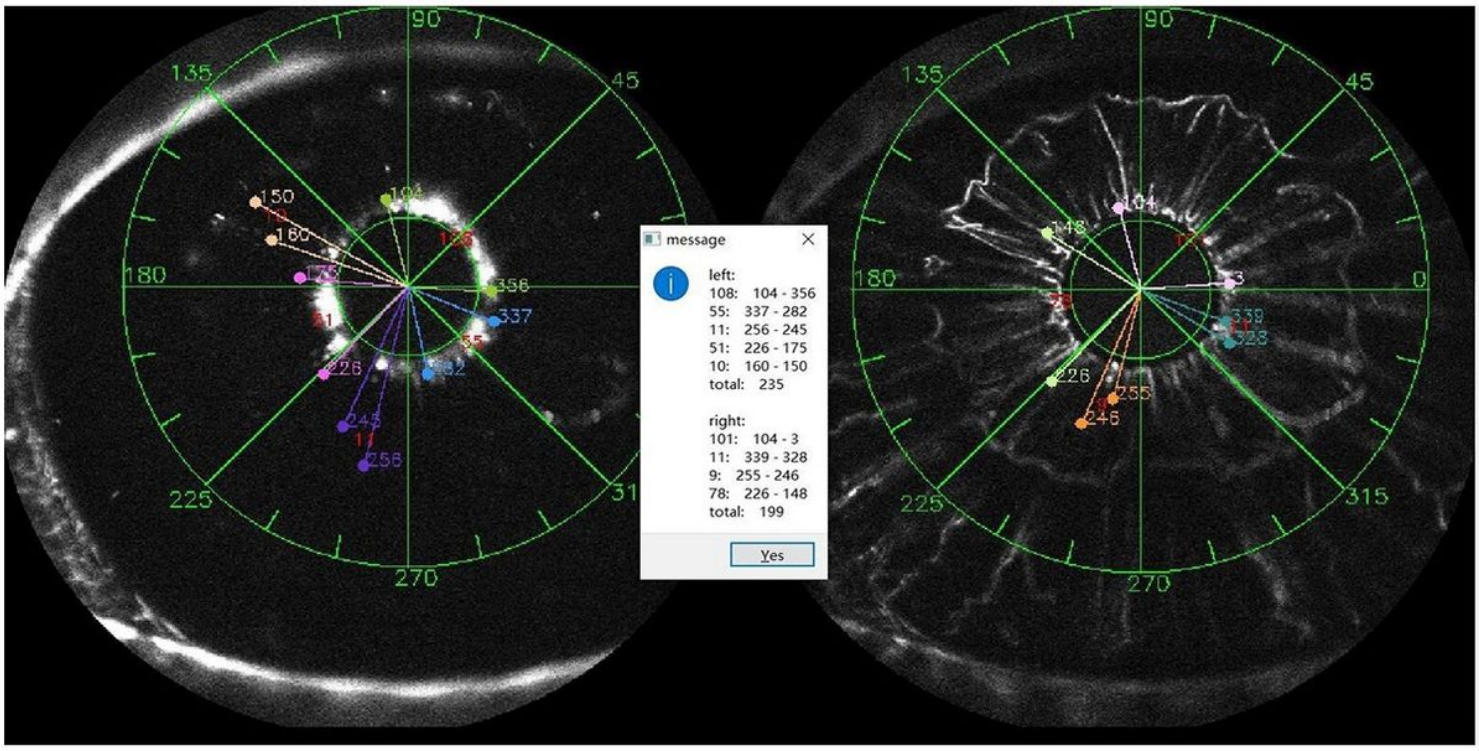

Figure 3

Calculation the total circumferences of all leakage lesions

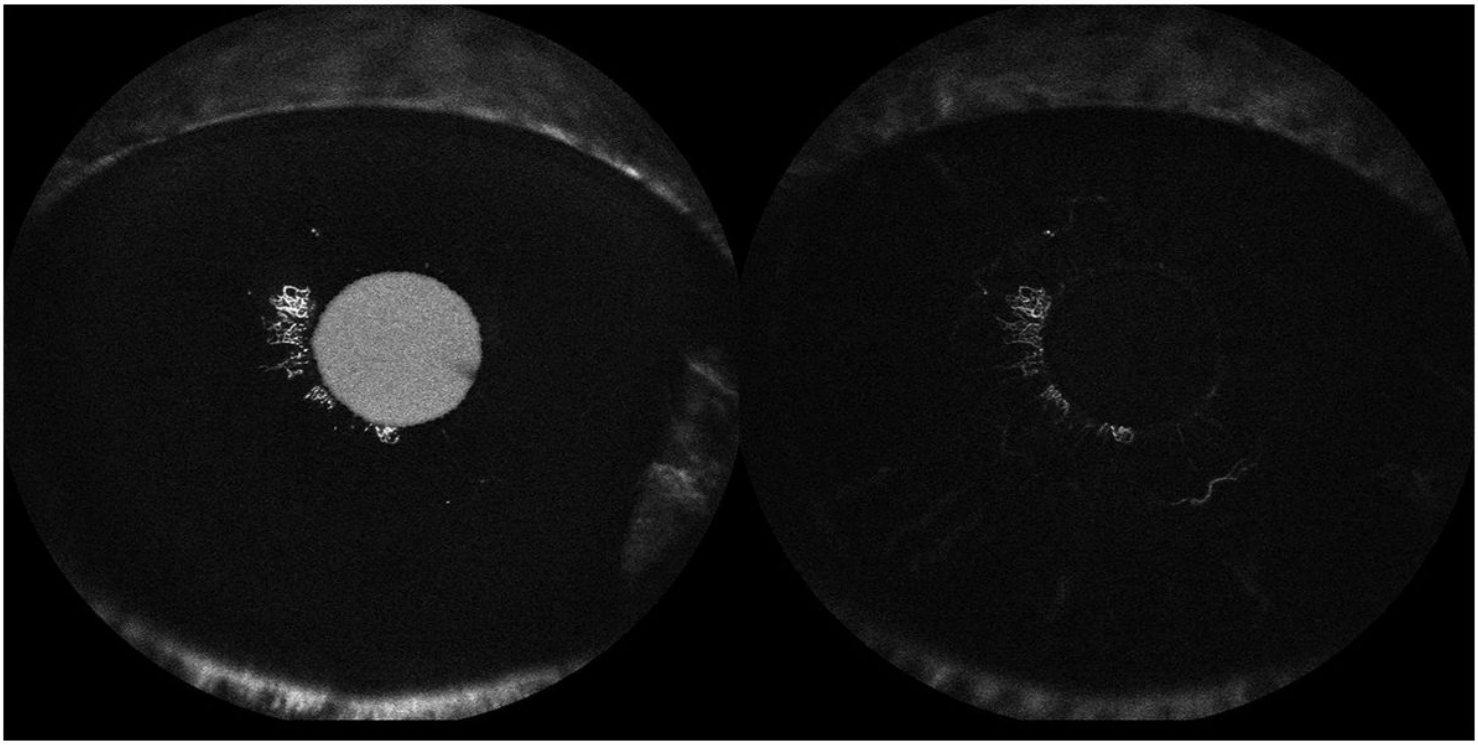

Figure 4

Early (20 s) imaging of IFA and IICGA in PDR patients with NVI.

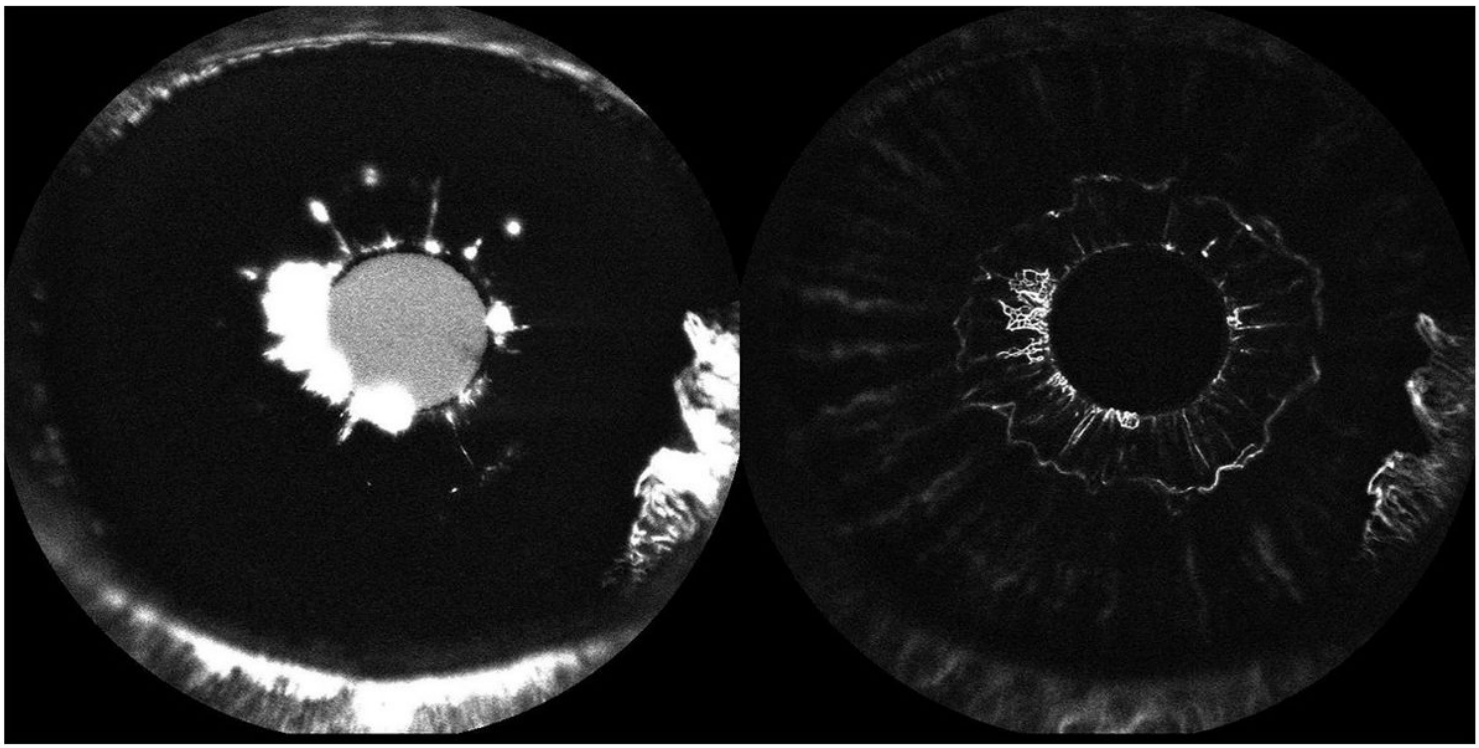

Figure 5

Late (40s) imaging of IFA and IICGA in PDR patients with NVI.