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Iris indocyanine green videoangiography in diabetic iridopathy

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Abstract

***Aims/Background*—Iris fluorescein angiography (IFA) is not commonly used in clinical practice, although its value has been demonstrated especially in cases of diabetic disease. IFA is able to show neovascular tufts in order to guide the laser treatment, and it is highly recommended in diabetic patients who need cataract surgery or vitrectomy. Nevertheless, IFA fails to demonstrate the iris vascular pattern in heavily pigmented iris and conspicuous leakage cases. The aim of the study was to evaluate the feasibility of iris indocyanine green videoangiography (IICGV) and to correlate its findings with those of IFA in diabetic iridopathy.**

***Methods*—Thirty six patients affected in varying degrees by diabetic retinopathy underwent an ophthalmic examination including retinal fluorescein angiography, IFA, and IICGV. IICGV was performed using IMAGEnet System H1024.**

***Results*—The results demonstrated that IICGV allows precise visualisation of the iris vascular pattern, also in cases of heavily pigmented iris.**

***Conclusions*—Three main findings seemed to be evident: firstly, iris neovascularisations are detected with IFA far more easily than IICGV; secondly, capillary dilatations and iris hypoperfusion are identified far more clearly using IICGV; thirdly, there is no evident relation between capillary dilatation or iris hypoperfusion, and degree of diabetic retinopathy.**

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Iris fluorescein angiography (IFA) is not commonly used in clinical practice, although several studies have underlined its importance in the detection of iris microvascular abnormalities. Its value has been demonstrated especially in the vaso-occlusive disorders, wherever IFA is able to show neovascular tufts and guide the laser treatment in an effort to avoid neovascular glaucoma development.[1 2] Moreover, it is highly recommended in diabetic patients who need cataract surgery or vitrectomy.[3 4]

Nevertheless, IFA often fails to demonstrate the iris vascular pattern particularly in cases presenting heavily pigmented iris or conspicuous leakage.

Indocyanine green videoangiography has been recently introduced in the diagnosis of several retinochoroidal diseases. The main advantages of indocyanine green molecule are the characteristics of spectral absorption and emission in the near infrared wavelengths, which allow transmission through ocular pigmentations, and the almost complete protein binding, which reduces leakage.

The aim of the study is to evaluate the feasibility of iris indocyanine green videoangiography (IICGV) and to correlate its findings with those of IFA in diabetic iridopathy.

Materials and methods

Sixty eight patients with diabetes mellitus were recruited to participate in the current study. Each patient was informed of the purpose of the research. Informed consent was obtained only from 36 patients, 32 patients (47%) refused the IICGV examination, judging it not to be useful.

The inclusion criteria were diabetes mellitus type I or type II. The exclusion criteria were: dioptric media opacities, causing difficulties in the examination of the fundus; other ocular diseases; topical miotic therapy; previous laser or surgical ocular therapy. Each patient underwent an ophthalmic examination including retinal fluorescein angiography, IFA, and IICGV. The clinical characteristics of all patients are summarised in Table 1. The mean age was 67·8 (SD 3·1) years with 22 males (61·1%) and 14 females (38·9%). The mean duration of diabetes mellitus was 14·2 (4·5) years. The diabetic retinopathy level was graded in a masked fashion according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy,[5] by means of ophthalmoscopy, standard fundus photography, and fluorescein angiography. In particular, we considered 11 patients with non-proliferative diabetic retinopathy (NPDR) (level 1–3), 13 patients with pre-proliferative diabetic retinopathy (PPDR) (level 4–5), and 12 patients with proliferative diabetic retinopathy (PDR) (level 6·5–7).

Nine healthy subjects without any kind of ocular pathology were considered as the control group. The mean age was 61·6 (5·7) years, with five males (55·5%) and four females (44·5%).

In all cases IMAGEnet System H1024 (Topcon Corp) was employed. A solution containing 25 mg of indocyanine green in 5 ml of

Table 1 Clinical characteristics of diabetic patients

Age (years) (SD)	67·8 (3·1)
Sex	22 Males (61·1%), 14 females (38·9%)
Diabetes mellitus type	28 (77·8%) Insulin dependent
Diabetes mellitus duration (years) (SD)	14·2 (4·5)
Visual acuity (SD)	0·61 (0·2)

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Table 2 Iris fluorescein angiography results

	Control (n=18)	*NPDR (n=22)*	*PPDR (n=26)*	*PDR (n=24)*
Not-e for h-p*	4/18	12/22	8/26	10/24
Hypoperfusion†	0/14	0/10	8/18	10/14
Capillary dilatations	0/18	6/22	8/26	10/24
Peripupillary leakage	14/18	16/22	26/26	24/24
Stromal leakage	0/18	4/22	14/26	12/24
Neovascularisations	0/18	0/22	0/26	12/24

*Not evaluable for heavily pigmented iris.
†Hypoperfusion was evaluable only in patients not having heavily pigmented iris.
NPDR=non-proliferative diabetic retinopathy.
PPDR=pre-proliferative diabetic retinopathy.
PDR=proliferative diabetic retinopathy.

Table 3 Iris indocyanine green videoangiography results

	Control (n=18)	*NPDR (n=22)*	*PPDR (n=26)*	*PDR (n=24)*
Not-e for h-p*	0/18	0/22	0/26	0/24
Hypoperfusion†	0/18	8/22	26/26	24/24
Capillary dilatations	0/18	22/22	26/26	24/24
Peripupillary leakage	0/18	0/22	0/26	0/24
Stromal leakage	0/18	0/22	0/26	6/24
Neovascularisations	0/18	0/22	0/26	12/24

*Not evaluable for heavily pigmented iris.
†Hypoperfusion was evaluable only in patients not having heavily pigmented iris.

aqueous solvent was injected intravenously. IICGV images were taken at 1–5 second intervals up to 5–10 minutes. According to a previous experience, we decided not to protract the examination to the further phases, as the only visible feature is represented by the progressive iris washout.[6]

Each angiogram was evaluated in a masked fashion by two authors (MBP, EB): agreement between the two authors was achieved in 95% of cases, a third author (DR) was consulted to define the uncertain cases.

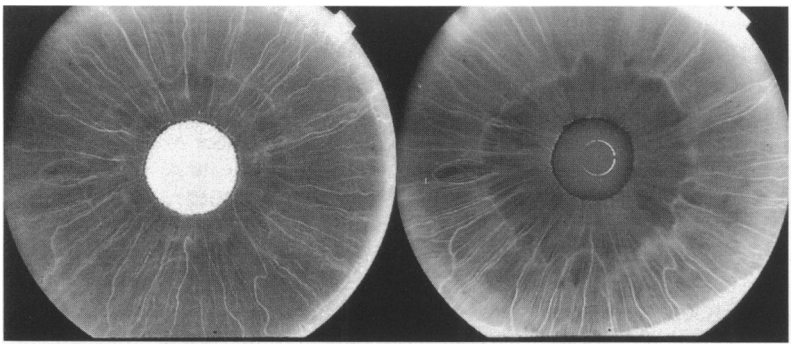

Figure 1 Control subject. Left: iris indocyanine green videoangiography (IICGV) frame showing a normal vascular pattern. Right: same eye using iris fluorescein angiography (IFA).

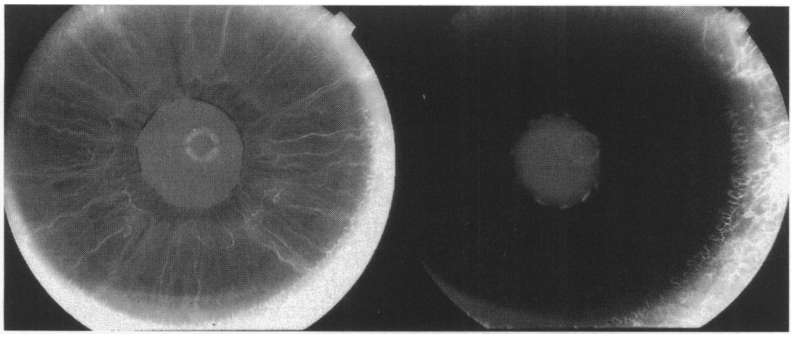

Figure 2 Patient with non-proliferative diabetic retinopathy. Left: IICGV frame showing several areas of hypoperfusion and capillary dilatations. Right: same eye using IFA. A mild peripupillary leakage only is evident.

Particular attention was drawn to detect differences between the two above mentioned techniques regarding imaging of heavily pigmented iris, hypoperfusion, neovascularisations, capillary dilatations, and peripupillary and stromal leakage.

Statistical analysis was carried out by means of the χ^2 test.

Results

In all the patients the pupillary diameter during examination was greater with IICGV than with IFA, even if the same flash power was used.

The results of 18 eyes of the control group are summarised in Tables 2 and 3. We noted a heavily pigmented iris in four eyes (22·2%). IFA showed a regular vascular pattern in all eyes except for the above mentioned four, where the vascular details were not visible. In no eyes was there evidence of hypoperfusion, neovascularisations, or capillary dilatations. In 14 eyes (77·8%) a mild peripupillary leakage was evident, consistent with the age of the patients (Fig 1).

In all the eyes of the control group, IICGV showed a regular vascular pattern, also allowing a precise evaluation of heavily pigmented iris. No signs of hypoperfusion, leakage, neovascularisations, or capillary dilatations were detected (Fig 1).

The results for the group of patients with diabetic retinopathy are reported in Tables 2 and 3. IFA failed to show the vascular pattern in 30 eyes (41·6%) with heavily pigmented iris (Fig 2). Considering the remaining 42 eyes, 18 eyes (25%) showed hypoperfusion areas of different extension (Figs 3 and 4). In particular, hypoperfusion was evident in no patients with NPDR, in eight eyes with PPDR, and in 10 eyes with PDR.

In 24 eyes (33·3%) we noted stromal capillary dilatations, six eyes corresponding to NPDR, eight eyes to PPDR, and 10 eyes to PDR, respectively.

In 66 eyes (91·6%) there was only a peripupillary leakage, 16 in NPDR, 26 in PPDR, and 24 in PDR, respectively. A stromal leakage was globally detected in 30 eyes (41·6%), four eyes with NPDR, 14 eyes with NPDR, and 12 eyes with PDR.

Moreover, in 12 eyes (16·6%) corresponding to PDR, peripupillary and stromal neovascular tufts were evident with late conspicuous leakage (Figs 3 and 4).

By means of IICGV we achieved a more precise evaluation of the vascular network in all the cases. In only two eyes with heavy black iris naevi was the resolution slightly reduced.

In 58 eyes (80·5%) there was evidence of iris hypoperfusion (Figs 2–4). In particular there were eight eyes corresponding to NPDR (8/22=36·3%), 26 to PPDR (26/26=100%), and 24 to PDR (24/24=100%). Whenever IFA showed iris hypoperfusion, IICGV demonstrated an extended hypoperfusion area (Figs 3 and 4). IFA failed to show hypoperfusion globally in 40 eyes – 30 eyes with heavily pigmented iris (Fig 2) and 10 eyes with normally pigmented iris (Fig 5).

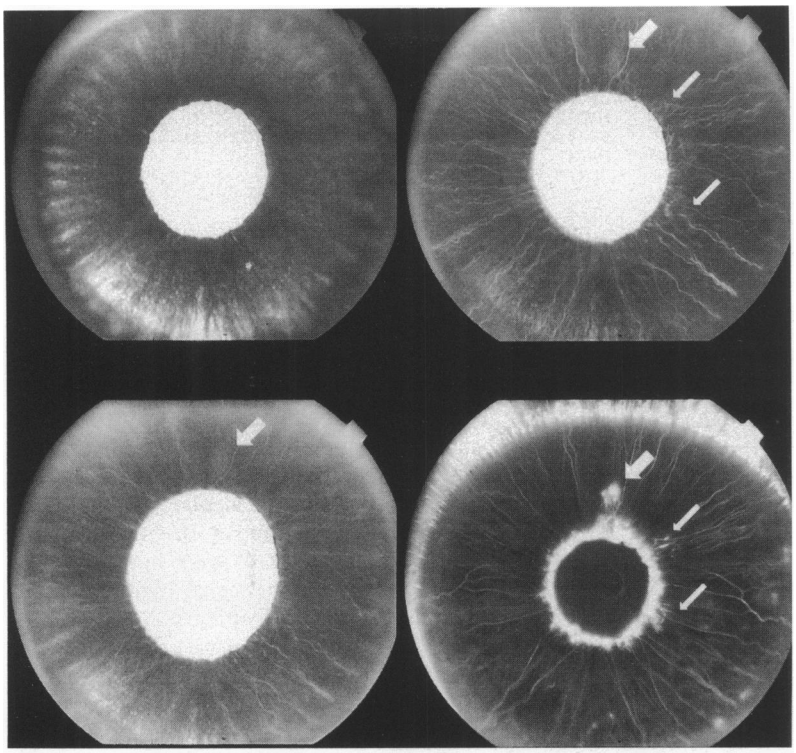

Figure 3 Patient with proliferative diabetic retinopathy. Top left: IICGV frame (12 seconds) showing hyperfluorescent lesions, especially in the inferior sector, before vascular filling. Top right: IICGV frame (28 seconds). The large arrow indicates a neovascular tuft and the thin arrows show capillary dilatations. In all the iris sector there is evidence of hypoperfusion. Bottom left: IICGV frame (about 2 minutes). The neovascular tuft shows a minimal leakage. Bottom right: IFA demonstrating a peripupillary and stromal leakage related to the neovascular tuft (thick arrow) and to capillary dilatation (thin arrows), in an iris showing hypoperfusion.

IICGV showed iris neovascularisations in the same 12 eyes (16·6%) shown by IFA. The neovascular tufts appeared as single hyperfluorescent spots or as an irregular plexus and were located along the border of hypoperfusion areas (Figs 3 and 4). A late and slight stromal leakage was detected in only six eyes (8·3%) showing neovascularisations (Figs 3 and 4).

In all the examined eyes (100%) we were able to detect several capillary dilatations. Moreover, 19 eyes (26·4%) showed hyperfluorescent lesions, with different size and shape, located close to the pupillary margin or in the iris stroma (Fig 3). The slit-lamp examination showed a degenerative process of the iris pigment epithelium of different degrees in the zones which appeared hyperfluorescent on IICGV. Thus, it seems that such a hyperfluorescence appears to be due to a mechanism of iris retroillumination which is related to the fluorescence of the dye in the retinochoroidal circulation.

The statistical analysis revealed a significant difference between IFA and IICGV with regard to the detection of hypoperfusion, capillary dilatations, peripupillary and stromal leakage ($p<0·001$).

Discussion

Our results indicate the IICGV allows precise visualisation of the iris vascular pattern in cases of heavily pigmented iris.

The greater pupillary diameter, seen on IICGV, may be directly ascribed to the characteristics of infrared spectral absorption and fluorescence.

A peculiar feature of IICGV is represented by the hyperfluorescent lesion detectable in 26·4% of eyes, which appears to be related to the iris pigment epithelium defect. The degenerative process of iris pigment epithelium represents a common phenomenon in several pathologies, and it was reported to be associated with diabetes mellitus in 30% of unselected cases.[7]

Diabetic microangiopathy may generally involve the ocular vascular system, but it especially affects iris and retinal vessels.[8]

In particular, the detection of a severe form of diabetic iridopathy (DI) or diabetic retinopathy (DR) contraindicates many ocular surgical treatments.

IFA was proved to be superior in the identification of DI to simple iris biomicroscopic examination.[3] Moreover, the detection of DI by means of IFA indicates the coexistence of DR in 93% of cases and the recognition of a proliferative DI suggests the presence of a serious PPDR or PDR.[4]

The typical IFA features of the DI are represented by capillary dilatation, peripupillary and stromal leakage, hypoperfusion, and neovascularisation development.[9] The assessment of the degree of DI by means of IFA is generally based on the leakage characteristics,[3 4 10] which may result both from a breakdown of the blood aqueous barrier or from iris neovascularisations. The evaluation of the other microvascular abnormalities is often difficult because of the iris pigmentation and/or the profuse leakage.

IICGV allows a more precise analysis of the iris vascular pattern, because it penetrates effectively through the iris pigmentation and it rarely causes minimal leakage, and then only in some cases of proliferative DI.

The typical features of DI on IICGV are mostly represented by the capillary dilatations and the iris hypoperfusion, because the imaging of the dye leakage and the iris neovascularisations are rather difficult.

The peripupillary leakage was evident in 91·6% and the stromal leakage in 41·7% of eyes with IFA, whereas by means of IICGV the leakage was really minimal and visible in only six (8·3%) out of the 12 cases with iris neovascularisation.

Iris neovascularisations appear on IFA as leaking tufts, whereas in IICGV they appear both as single hyperfluorescent spots and/or as an irregular plexus: the former correspond to capillary dilatations, and in the latter the focusing may be difficult. For these reasons we believe that the diagnosis of iris neovascularisations may be simpler using IFA rather than IICGV. The poor demonstration of iris neovascularisations on IICGV may be related to the strong protein binding of the indocyanine green molecule and the large protein complex to which indocyanine green binds, unlike the situation on IFA where there is a considerable free fluorescein.

Regarding capillary dilatations, IICGV reveals their presence in 100% of eyes, whereas IFA is able to show the same features in only 33·3% of eyes. Their numbers and locations do not seem to be linked to the severity of DR.

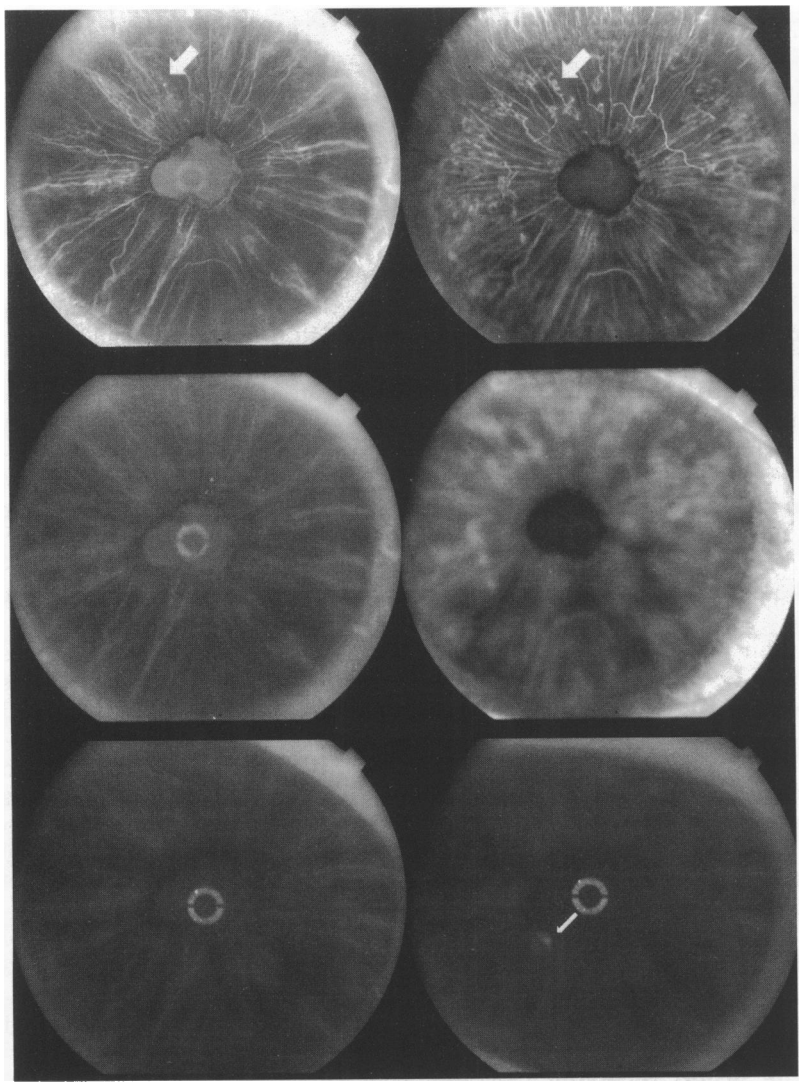

Figure 4 Patient with proliferative diabetic retinopathy. Top left: IICGV frame (49 seconds) showing a severe iris hypoperfusion with numerous neovascular tufts (arrow). Top right: IFA frame demonstrating hypoperfusion and neovascular tufts (arrow). Centre left: IICGV frame (about 5 minutes) with evidence of minimal leakage. Centre right: late IFA frame with conspicuous leakage. Bottom left and bottom right: late IICGV frames (10 minutes and 15 minutes respectively) showing the progressive dye washout. The arrow indicates an artefact.

Iris hypoperfusion results from a closure of the iris capillaries and IICGV allows its imaging in 80·5% of eyes, in comparison with 25% on IFA. It is always evident in cases of PPDR or PDR, but it is recognisable also in 36·3% of cases affected by NPDR. Moreover, iris hypoperfusion areas, whenever they are evident on both angiographic techniques, appear larger and are better delineated by IICGV. A marked iris hypoperfusion accompanies only iris neovascularisations, which we found in only 12 eyes with PDR. In the other cases a relation between extension of iris hypoperfusion and severity of DR was not evident. It is not surprising to find iris hypoperfusion in all the cases of PPDR or PDR, where retinal ischaemia exists; it is noteworthy, however, that IICGV detects iris hypoperfusion in 36·3% of cases with NPDR, where there is no evidence of retinal ischaemia.

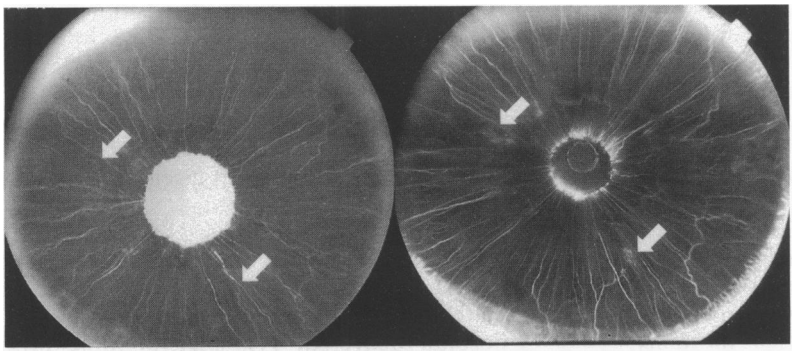

Figure 5 Patient with pre-proliferative diabetic retinopathy. Left: IICGV frame (25 seconds) showing iris hypoperfusion in the horizontal sectors and some capillary dilatations (arrows). Right: IFA frame showing no evidence of iris hypoperfusion, and demonstrating only a slight leakage from capillary dilatations (arrows).

Some studies showed the occurrence of the capillary closure process in the macular region in NPDR too, with consequent foveal avascular zone enlargement.[11–14]

Although the number of cases affected by NPDR was restricted, we searched retrospectively for a correlation between evidence of quantitative or qualitative abnormalities of foveal avascular zone and iris hypoperfusion, without achieving a positive result.

Therefore, capillary dilatations and iris hypoperfusion seem to be a manifestation of diabetic microangiopathy that are relatively independent from the severity of DR. Thus, the clinical value of capillary dilatations and iris hypoperfusion appears to be limited, indicating only an iris involvement by diabetic microangiopathy.

In conclusion, our research seems to indicate three main findings: firstly, iris neovascularisations are detected with IFA far more easily than IICGV; secondly, capillary dilatations and iris hypoperfusion are identified far more clearly using IICGV; thirdly, there is no evident relation between capillary dilatations or iris hypoperfusion, and degree of diabetic retinopathy.

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