Clinical Experience with Fluorescence Retinal Cinematography

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PHOTOGRAPHY of fluorescence in retinal vessels as described by Novotny and Alvis affords a means of studying the dynamic characteristics of the retinal circulation. Studies in our laboratory and by other investigators using this method or a modification have demonstrated retinal vascular phenomena that would be difficult to recognize by ophthalmoscopic visualization alone. The single film photographic technic, however, has the disadvantage of allowing exposures at relatively slow speeds. This necessitates multiple injections and grouping arrangements in order to complete a retinal vascular study.

In order to evaluate fully the moment-to-moment changes in the retinal circulation during various physiologic and pathologic conditions, a high-speed (up to 16 frames per second) photographic method was developed in our laboratory. This report will describe our observations in 70 patients studied by fluorescence retinal cinematography. The advantages and limitations of the method and the clinical and investigative applications will also be discussed.

Technic and Procedure

A Bausch and Lomb binocular ophthalmoscope and a modified Arriflex 16-mm. camera geared to run between 10 and 16 frames per second were adapted for this study. The details of the instrumentation have been reported elsewhere and will be only briefly reviewed.

The light obtained, from a 6-volt auto lamp increased temporarily to 12 volts, was focused and passed through a no. 47 (Kodak) blue Wratten gelatin filter (transmission, 420 to 470 millimicrons), and was then reflected into the ocular fundus. Light at this wavelength excites fluorescence of the injected dye. Light reflected from the retina passed through a no. 56 (Kodak) green Wratten filter (transmission, 510 to 560 millimicrons) to Kodak Cineflure film. This filter impeded transmission of most of the reflected blue rays from the nonvascular portions of the retina and increased the contrast between fluorescent and nonfluorescent areas.

Full dilatation of the subject's pupils and fixation of gaze are essential. A few feet of control film were exposed with only the green filter in the system. The blue filter was inserted, the camera started, and approximately 10 ml. of 5-per cent Fluorescine (Kirk and Company) were injected in an antecubital vein. Rapid transit through the venous system was encouraged by utilizing reactive hyperemia and a flushing technic. The moment of injection was indicated on the film by depressing a foot switch which momentarily extinguished the illumination.

The completed motion-picture study was examined in a Weinberg-Watson converted Kodak projector. This permitted different speeds of projection as well as single frame examinations. If more detailed analyses were desired, film strips could be printed on photographic paper.

Results and Comments

Normal Circulation

In the normal retinal circulation, as demonstrated in 15 patients, fluorescein appeared at the optic disc 8 to 10 seconds after injection into an antecubital vein. Arterioles in the macular region fluoresced first, followed quickly by the remainder of the arteriolar system. This arteriolar phase was usually com-
complete within 1 to 2 seconds. Fluorescein appeared initially in the central portion of the arteriole and was followed by complete opacification of the lumen. This “front” was characteristic of laminar flow. Immediately after the arteriolar phase, a faint diffuse background fluorescence appeared, which was probably due to fluorescein in retinal capillaries and the choroidal vessels. The first phase of fluorescence of the venous circulation appeared before the dye had completely filled the arterioles in the nasal portion of the retina. Fluorescence did not appear at the same moment in all of the small veins draining into a major venous channel. It might appear in one small vein as much as three seconds before it appeared in a similar sized companion vein. As the fluorescein-laden blood drained into a larger vein, fluorescence appeared along the lateral margin of the larger vein and streamed toward the optic disc. As more of the small veins draining into a larger vein contained fluorescein, the streaming effect became less apparent (fig. 1). As previously described by Dollery and his associates, streaming is abruptly disrupted at points of arteriovenous nicking where turbulence exists. Streaming in the veins was seen in all studies but was most prominent in patients with the slowest retinal blood flow. The phenomenon may be due to differences in velocity of flow through segments of the retinal circulation or to differences in the length of the vascular circuits in various areas of the retina.

The emptying of the veins followed a pattern opposite to the filling phase. Fluorescein disappeared first from the lateral margins of the veins as blood without fluorescein entered from the smaller veins. The retinal venous phase generally lasted 15 to 20 seconds. The retinal background fluorescence slowly faded and usually disappeared along with the loss of venous fluorescence.

Abnormalities in the Retinal Circulation

Diabetic Retinopathy

Histologic studies have demonstrated that many microaneurysms in diabetic retinopathy are not visible by conventional ophthalmoscopic examination. A greater number of such microaneurysms are visible by the fluorescein technic than by routine retinal photography (fig. 2). A significant number of such lesions was demonstrated in all but two of 12 diabetic patients studied. Diabetic patients also had vascular structures which appeared clinically to be microaneurysms but which did not fluoresce. Presumably, these structures were either small retinal hemorrhages or occluded aneurysms, as demonstrated on postmortem examination by Cogan and his associates. The capillary aneurysms were frequently seen in close proximity to flame-shaped hemorrhages that did not fluoresce and near soft exudates that did fluoresce. The microaneurysms usually filled during the late arteriolar or early venous phases. In contrast to the rest of the circulation, they appeared to have a prolonged emptying time and to retain fluorescence after the other vessels had been completely cleared of fluorescein. It is not known whether such prolonged fluorescence was due to slow circulation of the dye through these structures or to staining of the walls of the microaneurysms, which may have an increased affinity or permeability for fluorescein.

Narrowed and tortuous retinal vessels were seen in older diabetic subjects, consistent with

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Venous streaming. (This and subsequent figures are enlargements of a single frame from 16-mm. film run at 10 frames per second.) The arterioles and capillaries are fluorescent and the first phase of venous filling has begun. The fluorescein in the veins is seen streaming along the lateral margins and at the junction of two veins (arrow).
The retinal circulation time normally ranged from 15 to 20 seconds when measured from the first appearance of fluorescein in an artery to its disappearance in a corresponding vein. In four of six diabetic patients in which this could be measured, the time was prolonged (from 25 to 95 seconds) in the absence of any other factor that would tend to distort a dye curve. In one patient with mild diabetes of 9 years’ duration, it was prolonged 35 to 40 seconds, despite an otherwise normal retinal circulation.

**Hypertensive Retinopathy**

Ten patients with hypertensive vascular disease were studied. Arteriolar tortuosity and spasm were clearly seen by the fluorescein technic. Flame-shaped hemorrhages did not fluoresce. Exudates in more advanced stages of hypertension could be divided into two groups as regards fluorescence. Those that had the appearance of hard exudates did not develop fluorescence. The new, soft, or so-called cotton-wool lesions were noted to fluoresce brightly and to retain this fluorescence after the rest of the retinal structures had been cleared of dye. In many cases this would last for hours. As noted by Dollery, Hodge, and Engel, these lesions may be resorbed clinically during the course of treatment for hypertension, but fluorescence may still appear at the previous site. Also a fluorescent area can precede a visible soft exudate, demonstrating in each instance an increase in capillary permeability, which is otherwise not visible. It is not uncommon to see the area of fluorescence extend over a larger area than that covered by a visible exudate.

Malignant hypertension with papilledema presented a striking fluorescence. There was a marked increase in vascularization of the edematous nerve head and, subsequently, a diffuse fluorescence (fig. 3) which might last for hours. It appeared that there was a marked degree of capillary permeability in the area about the optic disc. The extent of the vascularization and diffuse fluorescence seemed to parallel the clinical severity of the papilledema. These vessels disappear as the papilledema regresses.
The vascular structures in a patient with Linden-von Hippel disease were difficult to see by ordinary ophthalmoscopy but were clearly demonstrated by the fluorescein technic. The structure seems to be a vast network with a diffusion of dye into the surrounding area. The fluorescence remained at least 5 minutes after the rest of the vascular structures had returned to normal.

It has been possible in other patients to demonstrate vascular disruption in areas of chorioretinitis and abnormal filling patterns in patients with vascular occlusions. The technic may be useful in distinguishing large retinal hemorrhages from tumors such as melanomas.

Figure 3
Papilledema secondary to increased intracranial pressure. Top. Early venous phase. The neovascularization of the disc is present and initial exudation of fluorescein is seen. Bottom. The major vessels are now cleared of fluorescein (dark lines) and diffuse fluorescence of the disc remains.

Miscellaneous Studies
Retinal cinematography was carried out in a patient with leukemia (fig. 4). On clinical grounds, the vascular lesions present were considered to be retinal hemorrhages. Injection of fluorescein, however, revealed some of these structures to be in continuity with the vascular system filling during the late arteriolar phase, presenting the appearance of diabetic microaneurysms. In contrast to the diabetic lesion, however, the fluorescence was of short duration, disappearing with the venous phase. Fluorescence did not appear in other similar lesions in this patient which may have been hemorrhages or occluded microaneurysms.

Figure 4
Microaneurysms in leukemia. Top. The dark punctate areas in this control film were dark red in vivo. Bottom. After fluorescein injection an appearance similar to diabetic microaneurysms is seen. These punctate areas of fluorescence disappeared with the venous phase.
Such a differentiation should be possible but experience is limited at the present time.

A fluorescein injection was carried out in a patient who had a "Hollenhorst plaque" in a retinal arteriole. The fluorescein injection demonstrated adequate, although delayed, flow past the plaque. These plaques often cause vascular occlusion.7

One of the first uses for fluorescein retinal cinematography was in the study of the effects of hypothermia and high- and low-flow cardiopulmonary bypass in the dog. The differences in the rate of flow under these various conditions were clearly evident.8

Discussion

Retinal cinematographic studies in our laboratory have demonstrated the value of this technic with use of filming rates up to 16 frames per second. The entire sequence of retinal flow is dramatically and continuously portrayed without resort to multiple injections and grouping arrangements necessary with the still photographic technic. The details of the finer vascular structures at present are better with the still technic, for the electronic flash permits the films to be exposed at 1/1,000 of a second. The detail of the cinematogram is usually satisfactory, however, so that rarely is it necessary to resort to the still technic. A still color photograph of the retina is essential for interpreting a fluorescent cinematogram. The still color photograph aids in orientation of the cinematogram. Even more important is recognition of structures that have failed to fluoresce (i.e., hemorrhages) or fluorescence that was not visible on the color photo (i.e., microaneurysms).

We are investigating methods of increasing the motion picture speed without loss of detail. This may be possible by improving the light source. Increasing the concentration of dye at the retinal site should also improve the detail. With use of an indwelling needle in conjunction with reactive hyperemia and a quick saline flush, a good bolus of dye reaches the retinal vessels in most patients. Other methods for insuring a high concentration of dye in the retinal vessels may be used in patients with larger blood volumes, low cardiac output, or polycythemia. Dollery and associates have used a polyethylene catheter in the superior vena cava or innominate artery2,5 with good results, and we have made direct injections into the root of the aorta.

Fluorescein cinematography has proved valuable in several ways. First of all, it has allowed us to evaluate the normal retinal circulation. That the flow in arterioles is laminar is clearly demonstrated. The streaming of fluorescein seen in large veins graphically demonstrates that the retinal circulation is composed of a number of segments, each of which may have different flow characteristics, depending on a difference in velocity of flow in certain segments or a difference in segment length.

This technic should lead to a more thorough understanding of the sequence of events in the pathogenesis of retinal hemorrhages, exudates, microaneurysms, vascular occlusions, and other disease states in which the consequences of vascular change may be manifest. The changes in the blood vessels in arteriosclerotic, diabetic, and hypertensive patients have been clearly demonstrated and flow characteristics were elucidated.

It also seems probable that the differentiation of retinal or choroidal hemorrhages from tumors such as melanomas may be possible. In fact, any vascular lesion of the retina or choroid, such as those with Lindau-von Hippel disease or vascular occlusions, may be photographed with this method. Follow-up studies after surgery can then be accomplished and the results evaluated.

The cinematographic technic offers an advantage in elucidating changes in caliber and especially flow in retinal vessels and indirectly in cerebral vessels under a variety of physiologic stimuli. Cinematographic technics permit an accurate timing of the various phases of the retinal circulation. The retinal circulation time has been measured as that time from the first appearance of dye in a retinal arteriole until its disappearance from a corresponding vein.

Generally, the injection of fluorescein produced no symptoms. In patients with fair complexions, a pale yellow hue was observed.
for 8 to 12 hours with subsequent discoloration of the urine for approximately 24 hours. In 10 per cent of our patients nausea and vomiting occurred within 1 minute of the injection and was usually associated with the larger doses (10 ml.). The nausea was usually transitory and subsided spontaneously within 5 minutes. Four milliliters of 5-per cent fluorescein injected into the root of the aorta produced no noticeable effects in one patient, and injections of the innominate artery have been well tolerated.3

Poor retinal cinematographs are occasionally produced for reasons other than those directly related to camera technic. Poor patient fixation or inability to cooperate, slow general circulation, and various cardiovascular disturbances may result in poor contrast films.

Summary

Clinical experience with fluorescence retinal cinematography in 70 patients is presented.

The sequence of normal retinal vascular filling is described. Of particular interest is the demonstration that the retinal circulation consists of a number of vascular segments, each of which may have different flow characteristics.

The pathologic alterations in patients with diabetic and hypertensive retinopathy, papilledema, and other disease states are discussed.

The dynamic portrayal of the retinal circulation, enabling moment-to-moment evaluation, and the efficiency of the cinematographic technic are distinct advantages over the single-film method.

References
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