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Fluorescein angiography of the retina

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Fluorescein Angiography of the Retina

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HISTORY AND TECHNIQUE

The problems of retinal vascular disease can be approached from one of two very different viewpoints. One can ask what are the systemic lesions and symptoms that are correlated with a given opthalmoscopic picture, or one can ask what precisely are the changes in the retinal blood vessels that are responsible for this or that opthalmoscopic finding. The latter approach is especially inviting because of the unique quality of transparency in the eye, thus allowing direct observation of the retinal vessels. Thus, techniques have been developed for measuring changes in caliber of retinal vessels, for observing retinal blood flow by cinematography, etc., but these methods have certain limitations.

In 1961, Novotny and Alvis introduced the use of intravascular fluorescein and retinal photography to improve the visibility and definition of retinal blood flow. At that time they described separate arteriolar and venous filling phases, an arteriolovenous shunt, sluggish choroidal circulation, stratified flow of fluorescein, and rapid central retinal circulation times. They also described neovascularization and cotton-wool patches, but found that hemorrhages did not fluoresce.

In 1962, Dollery, Hodge and Engel described the distinct phases of the passage of fluorescein through the retinal vasculature. First, comes the <u>early arteriolar phase</u> as the retinal arterioles rapidly fill within one second or so of the dye's appearance at the disk (generally 12 to 30 seconds after injection). Two to three seconds later the peak concentration of dye reaches the arterioles

and the late arteriolar phase is encountered, during which the entire arteriolar tree is brightly fluorescent. The capillary phase is evidenced by a generalized background fluorescence, and often even individual capillaries can be identified. During the early arteriolar phase, some dye passes rapidly across the capillaries into the small veins. At the late arteriolar stage, fluorescein is already entering the main retinal veins from tributaries near the disk. Streaming is noted in these veins secondary to the laminar flow reported by Novotny and Alvis. The early venous phase is most prominent at the macular region, due in part to the shorter circulation pathway. This results in a wider column of dye being present on the macular side of the temporal veins. Fifteen to twenty seconds after the first appearance of the dye, the arterioles lose their fluorescence and the late venous phase begins, with a wider band of fluorescence on the side of the temporal veins away from the macula. Most background fluorescence disappears by the late venous phase except at the disk, where it persists for several hours.

With the increasingly widespread use of fluorescein angiography, Haining and Lancaster in 1967 described modifications of the Zeiss fundus camera for rapid serial photography (previously, one could take pictures every twelve seconds), an improved filter system and a new mechanical injection system. To study the retinal circulation accurately, one needs a high initial concentration of fluorescein and fast consecutive photography. The basic unit used is a Zeiss fundus camera with a high power, rapid recycling, flash generator, with a most rapid sequence of 0.6 seconds. A clock and

inscription area is incorporated into each picture, and an objective lens is added to create a larger field. Kodak Tri-X film is used and is developed at 68 F. in D-11 diluted 1:1.

In retinal angiography a filter system must be incorporated to exclude the exciting light from the camera plane and yet allow a high percentage of transmittance in the desired wavelength of the fluorescent emission, thus producing a high degree of contrast. Studies have shown the peak excitation wavelength to vary from 4600 to 4800 angstroms, while the peak emission spectrum is constant at 5200 angstroms. Interference filters reportedly are much better than absorption filters in excluding unwanted exciting light and allowing 90% transmittance of fluorescence.

Arterial injection of fluorescein allows a sharper dye front to enter the choroidoretinal circulation, but the hazards of intra-arterial catheterization are high, and thus intravenous injections are used with a small bore syringe or short catheter. In order to get a more standardized injection and to improve the rate of dye injection, a mechanical injector may be used. This system also allows one operator to perform the entire angiography. As might be expected, a fast circulation time favors a more compact "dye curve" and better quality photographs, whereas a slow circulation time (as in heart failure, valvular incompetence or intracardiac shunts) produces weak flyorescence over a longer period. Results are especially good in patients with severe anemia due to a shortened circulation time and less absorption of dye by the blood.

Linhart et.al. have described the use of a high speed (up to 16 frames per second) photographic method i.e. fluorescence retinal

cinematography. This allows a more dynamic study of retinal flow and more clearly demonstrates the laminar flow in arterioles and the streaming seen in large veins, thus leading to the conclusion that the retinal circulation is composed of a number of segments with varying flow characteristics. This technique, however, does not show the finer vascular structures as well as the still technique.

Few complications are encountered with fluorescein angiography. The patient should be warned that his urine may be bright yellow for a few hours and that a transient yellowish discoloration of the skin may develop. A few also experience nausea, vomiting, syncope, pyrexia, irritation of tissues secondary to extravasation and possible thrombophlebitis. A rare anaphylactoid reaction has also been reported, and thus it is recommended that an emergency tray be kept close at hand.

GENERAL CLINICAL APPLICATIONS

A wide range of phenomena can be elicited by fluorescence fundus photography, including processes involving the retina, optic disks, or choroid. Where the individual vessels are clearly visible, in the retina and on the disk surface, one can study the outline of the vessels and abnormalities such as aneurysms and new formed vessels may be seen. Gross disturbances of the flow rate may also be detected, as well as leakage of fluorescein from the vessels. In considering such leakage, one must consider it as evidence of a damaged vessel only for the first, fast passage of the dye bolus through the arteries-capillaries-vein cycle. With repeated passage of the dye through the retinal vasculature (after the first thirty seconds), it becomes rapidly diluted and leaves the capillaries in the process of normal capillary-tissue fluid exchange.

The disk has both surface vessels and a vascular bed within its substance. The latter shows only bulk fluorescence except in papilledema when the engorged vessels may become individually visible. This pattern may also be modified by drusen.

The choroidal circulation is not directly visible because of interposed tissues, but it does contribute to normal background fluorescence. The principal element masking choroidal fluorescence is the retinal pigment epithelium, but abnormal elements may also mask this fluorescence of which the most potent is blood. In retinitis pigmentosa and some instances of choroiditis, patches of increased background fluorescence can be seen, with dense shadows corresponding to the pigment clumps. Thus, in the choroidal circulation, the pattern of staining is determined by the "windows" provided by disease, and leakage occurs when the "glazing of the windows" is defective so that fluorescein can spread in front of the masking pigment epithelium, together with the other products of exudation.

Summarizing the above noted phenomena one can detect with fluorescein, we find:

Retina--Anatomical changes
Altered flow
Leakage

Optic disk--Dilatation of vessels
Changes in bulk fluorescence

Choroid--New vascular systems (tumors)
Unmasking, disturbed retinal pigment epithelium
Leakage

The success of fluorescein retinal angiography in disclosing these phenomena depends on three characteristics of the retinal

circulation: the circulation is confined almost to one plane, it has low permeability to fluorescein, and it is set against a curtain of pigment epithelium.

Rubinstein and Paton have stated that fluorescein seems to be "mopped up" by some tissues to the point of photogenicity and not by others, and that all these tissues seem to be abnormal with the exception of the sclerae. Other stainable elements seem to be either organizing transudates,or young repair tissue, or formed scars, or areas of degeneration. These doctors have also made certain clinical conclusions, including:

(1) late fluorescence is extravascular

(2) neither pigment or hemorrhage take up fluorescein

(3) so-called late leakage of fluorescein from new vessels seems to come in fact from the glial or fibrous stroma accompanying them, which selectively takes up fluorescein from the body fluids

(4) micro-aneurysms which fluoresce during the vascular phase (first thirty seconds) are true distensions or sacculations, and maintain prolonged fluorescence not due to stagnation but due to absorption of the dye by the atheromatous plaques in the aneurysms wall

(5) late spotty stain in areas of vascular embarrassment signifies degenerative deposits and repair, not connected directly with the vascular tree

(6) Bruch's membrane itself does not stain but the drusen do and they contribute to the spotty stain of the fundus

(7) fluorescein technique is useful in differentiating macular lesions, as hemorrhage and pigment do not stain, while post inflammatory or degenerative macular mounds stain in an escalating manner

and tumors fluoresce in a mottled way from the start and fade away later.

SPECIFIC CLINICAL FINDINGS

After considering the above noted general clinical applications, it is now time to proceed to some definite clinical entities and their appearance with fluorescein angiography as described by Gass.

Acute loss of central vision may be due to embolic obstruction of the central retinal artery, a cilioretinal artery, or any one of their peripheral arteriolar branches supplying the macular region. Fluorescein angiography is helpful in establishing the presence or absence of arterial obstruction, the site and degree of obstruction, and the presence or absence of collateral flow. In the normal patient, one sees a background choroidal flush just prior to the appearance of fluorescein in the central retinal artery branches on the optic nerve head. If cilioretinal arteries are present, dye appears in them simultaneously with the choroidal flush, and some of the optic nerve head capillaries also fill. Perfusion of the macular vessels is rapid and occurs prior to complete filling of the remaining retinal vessels. Alterations of these major flow patterns can be seen readily with serial angiography. In most cases some fluorescein is seen in the artery distal to the block because of "seepage" by the embolus or collaterals, but a significant reduction in flow time is present. The dye column in the partly blocked area is often irregular in caliber and density and usually more concentrated then the dye in a similar sized normal vessel. The capillary bed often fails to fill, and fluorescein typically leaks from the arterial wall at the site of the embolus. Initially, the collateral capillary flow around an arterial block may be

difficult to demonstrate, but later these capillaries become dilated and tortuous. Thus, with acute embolic retinal artery obstruction, one sees alterations in intravascular blood flow, the normal vascular pattern and vessel permeability. Fluorescein angiography can also serve to monitor the effectiveness of various therapeutic measures in relieving the obstruction.

Loss of central vision may also be secondary to obstruction of any portion of the retinal venous network draining the macular region. The site of this obstruction may be the central retinal vein, a branch vein at an arteriovenous crossing, or rarely, in a small venule draining the macula. Low grade chronic obstruction results in cystoid macular edema. Angiography demonstrates an increase in retinal circulation time distal to the site of obstruction. Arterial filling time is normal in branch vein obstruction, but delayed in central vein obstruction. Capillaries distal to the block are generally dilated, tortuous and microaneurysms may appear. Leakage of dye from the capillaries and veins distal to the obstruction is characteristic. This dye pools in the perivascular region and imparts a glow around the vessels. The fluorescein also stains the extracellular serous exudate within the cystoid spaces and gives a characteristic pattern. If the venous obstruction is rapid in onset and marked in degree, massive intraretinal extravasation of blood and exudate may result in hemorrhagic infarction of the retina. Early angiography in this case may show only a large nonfluorescent area where the blood obscures the retinal and choroidal circulation, and also any dye leakage into the retinal tissue. Later, the intraretinal extravasation of dye may be evidenced

by the extension of dye beyond the area of hemorrhage. As breakdown of blood pigment occurs, the alterations in vascular pattern and permeability become more apparent. Following this hemorrhagic infarction, retinal atrophy may occur as evidenced angiographically by loss of retinal capillaries, development of prominent collareral channels, some narrowing and sheathing of the arteries and veins in the obstructed area, by possible neovascular proliferation into the vitreous, and microaneurysm formation. Leakage of fluorescein in this area of thinned atrophic retina is also seen.

Fluorescein can also be useful in investigating the fundiscopic picture of hypertension. Patients with so-called benign hypertension and grade I or II retinopathy show little angiopathy other than generalized narrowing of the arteries and capillary bed. Those presenting with a loss of macular function, however, virtually always show alterations of the structure and permeability of the fine retinal vascular bed, even when these changes are not seen with an opthalmoscope. These changes are often most prominent extramacularly, especially near the optic disc and large retinal vessels around the macula. In addition to the generalized narrowing of the arterial tree, one sees venous flow changes at arteriovenous crossings, focal areas of decreased capillary perfusion, tortuosity and irregular dilatation of capillaries, including microaneurysm formation, and leakage of dye from dilated capillaries and from precapillary arterioles. The focal areas of poor capillary perfusion may or may not correspond with cotton-wool patches, and the dilated capillaries and microaneurysms are often arranged in a wreath-like fashion around these areas. Focal areas of ischemic whitening of the retina (cotton-wool patches) have a characteristic angiographic pattern. Early, the lesion typically appears as a nonfluorescent

area, but sometimes may appear to stain with fluorescein due to reflected light from their white surface. Surrounding these patches are dilated capillaries showing multiple bead-like microaneurysmal changes, and dye may leak from these altered capillaries into the cotton-wool patch during the late stages of angiography. Waxy hard exudates are frequently seen in the extramacular region or aligned in a star figure in the macula, and do not stain with fluorescein. The patches of poor capillary perfusion are generally adjacent to the retinal arteries and appear to be the result of blockage of first and second order arterioles. Small hemorrhages, resulting from the rupture of the dilated capillaries and microaneurysms,produce nonfluorescent areas. New retinal vessels may form in hypertensive retinopathy and extend onto the inner surface of the retina, or into the vitreous (retinitis proliferans) and tend to leak fluorescein.

Angiography may also be helpful in demonstrating complications of hypertensive retinopathy such as small branch vein and branch artery obstruction, and serous detachment of the retina. In branch arterial obstruction, one sees dilated collateral channels. Branch venous obstruction at arteriovenous crossings is a frequent complication and has been discussed previously as far as angiographic findings. Serous detachment of the macula is an uncommon complication, except with severe hypertension of short duration as in eclampsia and collagen vascular disease. With this, one sees multifocal areas of dye leakage from the choroid into the subretinal fluid.

Fluorescein angiography can be quite useful in studying diabetic retinal changes and their effect on macular function.. It is true

that most diabetics who develop visual symptoms will have ophthalmoscopically visible changes in the retina, but a few may present with loss of visual acuity and little or no ophthalmoscopic changes, and it is in such cases that fluorescein angiography of the macula region will help to define the cause. The earliest angiographic finding is the development of capillary microaneurysms. Early, these are predominate on the venous side, but later they occur anywhere along the capillary wall as well as the terminal arterioles. These microaneurysms are usually round, but may be fusiform or cylindrical in shape. They are scattered at random in the macular and paramacular regions, without any particular relationship to the major retinal vessels, as opposed to the picture seen in hypertensive retinopathy. A few aneurysms fail to fluoresce because of stagnation or coagulation of blood within them, and thus resemble a punctate hemorrhage angiographically. These aneurysms may lead to focal capillary closure and the development of dilated, tortuous shunt capillaries. Varying degrees of fluorescein leakage develop in these microaneurysms and dilated shunt capillaries. The former characteristically develop an enlarging halo surrounding the aneurysm which tends to differentiate them from drusen of Bruch's membrane, which also appear as a round area of hyperfluorescence during the early stages of angiography. These permeability changes in the capillary bed and the degree of serous exudation into the retinal extracellular space in the macular area are variable factors and are important in loss of macular function. Fluorescein stains this serous exudate and thus defines the degree of expansion of the normally nonexistent, retinal extracellular space. Those diabetics with greater exudation have greater visual loss. One

usually sees partial loss of retinal transparency and intraretinal deposition of yellowish or waxy exudate accompanying extensive macular serous exudation. One also sees thickening of the retina and loss of the normal foveal depression, secondary to cystoid accumulation of exudate in the outer retinal layers. Reduction of the amount of serous exudate in the macula leads to improved central vision in most cases. A few patients lose their macular function from focal loss of perifoveal capillary bed, rather than retinal exudation. Angiography may also demonstrate a delay in fluorescein transit time through the capillary bed, especially in those patients with neovascular proliferation on the optic nerve head or retinal surface.

The above noted changes can be demonstrated angiographically prior to the development of severe ocular complications of diabetes, such as retinitis proliferans, vitreous hemorrhage and retinal detachment. Thus one may diagnose the cause of loss of central vision in those diagnostic problems which do not present with the above obvious signs. Angiography may also prove useful in establishing criteria for light coagulation treatment in certain patients who demonstrate vascular leakage which is largely confined to the paramacular region on the temporal side of the macula. It has already proven useful in detecting areas of new vessel growth onto the anterior surface of the retina prior to photocoagulation therapy. Angiography also offers promise as a valuable tool for studying the natural course of diabetic retinopathy, and the effect of therapy including medical, light coagulation and hypophysectomy on the natural course of the retinal changes.

Fluorescein angiography is also useful in the study of various other macular dysfunctions including retinal telangiectasis, secondary to irradiation of the orbital areas, unilateral carotid artery obstruction, collagen vascular disease and vitritis. I refer the reader to Gass for a description of the angiographic findings in these conditions.

SUMMARY

What I have attempted to do in this ophthalmologically oriented paper, is to acquaint the reader with the recently discovered and rapidly expanding field of fluorescein angiography. I have proceeded from a consideration of the history and technique of this process, to a discussion of its general clinical applications, and finally to a short description of the use and findings with this technique in some of the more common macular dysfunctions. Although this is a technique employed by those physicians specializing in diseases of the eye, I believe all doctors should at least be aware of its presence and applications in more precisely studying the fundus, the visualization of which is part of every good physical examination.

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