Fluorescein Angiography

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Learning Objectives
- Understand basic principles behind FA
- Explain common complications associated with FA
- Identify normal features of FA imaging
- Identify pathological patterns of hyperfluorescence and hypofluorescence

Fluorescein Angiography

Applications
- Diabetic retinopathy
- Age related macular degeneration
- Central retinal vein occlusion
- Branch retinal vein occlusion
- Central serous chorioretinopathy
- Cystoid macular edema
- Hypertensive retinopathy
- Central retinal artery occlusion

Should only be performed if the findings are likely to influence management

History
1871: Fluorescein was synthesized by Nobel laureate Johann Baeyer
1881: Ehrlich observed fluorescence in the anterior chamber after an injection of fluorescein
1950s: Flock and co-workers investigated methods to determine retinal circulation times with various dyes, including fluorescein
1961: Fluorescein was introduced to ophthalmic imaging by Novotny and Alvis (2 medical students)

What’s the Science?
When light energy is absorbed into a luminescent material, free electrons are elevated into higher energy states. This energy is then re-emitted by spontaneous decay of the electrons into their lower energy states. When this decay occurs in the visible spectrum, it is called luminescence.

Peak Absorption: 490nm
Peak Emission: 520nm

Excitation and Barrier filter
Two filter system:
- Excitation filter: transmits 490nm which is the absorption peak of fluorescein excitation
- Barrier filter: transmits 520nm which is the emitted peak of fluorescein

When choosing a camera, one should request the transmission curve of the filter combination to make sure that no significant overlap exists. (otherwise other items would “fluoresce”)

After several years, the filters become thin, emitting more light and increasing the incidence of pseudofluorescence.

**Fluorescein Solution**

Sodium Fluorescein C_{20}H_{12}O_{5}Na

- Orange-Red crystalline hydrocarbon
- When injected 80% is bound to protein, 20% remains in free bloodstream
- It is eliminated by the liver and kidneys within 24 hours, though traces may be found in the body for up to a week
- Available solutions:
  - 10mL of 5% fluorescein
  - 5mL of 10% fluorescein
  - 3mL of 25% fluorescein
- The larger the volume, the longer the injection
- The smaller the volume, the more solution remains in the venous dead space between the arm and the heart

Alternative if venous line could not be established or injection is refused:
- Oral administration of dose 30mg/kg
- Won’t see rush of fluorescein enter the eye
- Pictures are taken 20-60 minutes following ingestion

**Complications**

<table>
<thead>
<tr>
<th>Mild Reactions &lt;5%</th>
<th>Injection site reaction</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>Vomiting</td>
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<thead>
<tr>
<th>Moderately Severe Reactions &lt;1%</th>
<th>Urticaria</th>
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<tbody>
<tr>
<td>Shortness of breath</td>
<td>Vestovagal reaction</td>
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<td>Skin necrosis</td>
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<tr>
<th>Life-threatening reactions (&lt;0.001%)</th>
<th>Anaphylactic shock</th>
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<td>Seizure</td>
<td>Cardiovascular collapse</td>
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- Avoid angiography in pregnant women, especially in the first trimester
- Premedication with antihistamine and/or corticosteroids can be used for patients with a history of moderately severe reactions. (depending on the situation)
- All units performing fluorescein angiography should have a crash cart available

**Extravasation of fluorescein under the skin**

- Accidental administration of fluorescein into the extravascular space/tissue around the infusion site
- Side effects:
  - Can be extremely painful
  - Necrosis and sloughing of skin (rare)
  - Subcutaneous granuloma (rare)
  - Apply ice pack

A common cause is the use of a large, long needle directly attached to a syringe.
*Use scalp vein needle instead

**Procedure**

**Explanation: PARQ**

- Procedures
- Alternatives
- Risks
- Questions

**Material:**
- Fundus camera and auxiliary equipment
- Matched fluorescein filters (barrier and excitation)
- Digital photoprocessing unit (computer-based) and software user interface
- 23 gauge scalp vein needle
- 5 mL syringe
- Needle to draw the dye
- Armrest for fluorescein injection
- Tourniquet
- Alcohol swabs
- Bandage
- Standard emergency equipment

**Emergency Kit:**
- Airway bag
- Automated external defibrillator
- Oral or intramuscular antihistamines
- Autoinjectors for epinephrine

**Set up:**
- Maximal dilation
  - 6mm or more is best
- Preparation of fluorescein and scalp-vein needle
- Identification photo
- Set up patient
- Color photos
- Red free photos
- Filter in place, flash and camera ready
- Check which eye is the transit eye
Procedure

- Establish a venous line
- Start timer and inject 5mL of 10% Fluorescein rapidly (~10 sec)
  - Make sure not to overload the vein and inject the fluorescein under the skin
- Fluorescein should start appearing in the eye in about 8-12 seconds
  - 8 seconds for younger individuals
  - 12 seconds for older individuals
- Take photos every 1.5-2 seconds in the transit eye for about 30 seconds until the initial transit is complete
  - After, the fluorescein recirculates and the concentration of fluorescein begins to decrease
- Option of taking photos of fellow eye & periphery
- Wait (for late staining) ~3-5 minutes, take additional photo
- Option of taking 10 minute photo

Early phase

CHOROIDAL FLUSH (8-12s): choriocapillaris leaks dye freely through the space. Usually little detail as the RPE acts as an irregular filter that obscures view of choroid. When present, cilioretinal arteries fill at the same time.

ARTERIAL PHASE (2s after the choroidal phase): Retinal arteries fill

ARTERIOVENOUS PHASE: When the retinal arteries, capillaries, and veins contain fluorescein. The early part of this phase is the laminar phase when fluorescein is visualized in the walls of the larger veins.

Ateriovenous phase

Laminar phase when the fluorescein is in the laminar walls of the vein.
Early phase

VENOUS PHASE (about 30 s after injection): as the fluorescein leaves the arteries, the veins have an increase in fluorescein. Perifoveal capillary network best visualized during the venous phase.

Normal Macular Filling

Dark macula area:
- Taller, more pigmented RPE
- Xanthophyll pigment
- Absence of retinal capillaries in foveal center

Mid phase

Mid Phase: Recirculation occurs 2-4 min after injection. The arteries and veins are roughly equal in brightness.

Review of Vasculature

Retinal circulation supplies the inner 2/3 of the retina
- Non-fenestrated
- Blood-retinal barrier via tight junctions

Choroidal circulation supplies the outer 1/3 of the retina
- Fenestrated, low resistance
- Blood-retinal barrier via tight junctions at the RPE

Late Phase

Late Phase: Gradual elimination of the dye from the retina and choroid. Staining of the optic disc is normal. Photos normally taken 7-15 min after injection.

Review of Vasculature

Sodium Fluorescein readily diffused through the fenestrated vessels of the choriocapillaris but does not pass through healthy endothelial cells of non-fenestrated retinal vessels or through the RPE.
**Hypofluorescence**

- Reduction or absence of normal fluorescence
- BLOCKAGE
  - Hemorrhage
  - Pigment
- VASCULAR FILLING DEFECT
  - Absence of vascular tissue or by a complete or partial obstruction of the vessels

**Key:** correlate the hypofluorescence on the angiogram with the fundus view. If the size/shape/location corresponds, it's blockage. If not, it is a vascular filling defect.

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**Preretinal hemorrhage causing hypofluorescent blockage of all retina and choroid**

**Intraretinal hemorrhage causing blockage.**

**Subretinal hemorrhage causing hypofluorescence.**

**Subretinal hypertrophy of the retinal pigmented epithelium.**

**Blocked choroidal fluorescence and normal retinal fluorescence.**
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**Hyperfluorescence**
- Abnormally excessive fluorescence
  - PREINJECTION FLUORESCENCE
    - Pseudofluorescence
    - Autofluorescence
  - EARLY (vascular)
    - Retinal
    - Abnormal vessels
    - Choroidal
    - RPE window defect
    - Abnormal vessels
  - LATE (leak, extravascular)
    - Leakage
    - Neovascularization
    - Pooling
    - Staining
    - Tumors

To determine the type of hyperfluorescence, we must determine the time at which the hyperfluorescence appears.

**Pseudofluorescence**
- Pseudofluorescence (fake fluorescence)
  - Nonfluorescent structures appear fluorescent
  - Causes decreased contrast and resolution

Therefore, the two filters should be carefully matched so that the overlap of light is minimal.

**Autofluorescence**
- Occurs naturally in some pathologic entities
  - Optic disc drusen
  - Astrocytic hamartomas
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Fluorescein empties almost completely from retinal vasculature and choroid about 10-15 minutes after injection. Normal staining:

1. Fluorescence of the disc margins
2. Fluorescence of the lamina cribosa
3. Fluorescence of the sclera at the disc margin (scleral crescent)
4. Fluorescence of the scleral in a lightly pigmented fundus

Hyperfluorescence
Abnormally excessive fluorescence

- EARLY and LATE Defect:
  - Hyperfluorescence due to abnormal choroidal vessels: choroidal neovascularization.
  - Early fine lacy hyperfluorescence from the choroidal neovascularization.
  - Late leakage of the vessels.

- Leakage: dye is leaks from an intravascular space into an extravascular space
  - The area of leakage increases in size and intensity as the angiogram progresses
- Pooling: dye fills an anatomical space
  - Cysts, subretinal space, etc
- Staining: deposition of dye within involved tissue
  - Normal: optic nerve & sclera
  - Pathologic: scars

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Hyperfluorescence

**Early & Late Defect**

Disc leakage from optic disc swelling.
Early hyperfluorescence from dilated vessels
Late leakage. Dilated vessels leak.

Hyperfluorescence from leakage

**Cystoid macular edema with a petaloid appearance**

Hyperfluorescence: pooling of subretinal fluid

**Early and Late Defect**

Choroidal leakage and pooling into subretinal space
Early phase shows small hyperfluorescent spot
Late phase show pooling of the fluorescein. With pooling there is a defined space so the fluorescein will stop at the border of the central serous retinopathy.

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Hyperfluorescence: pooling of subretinal fluid

**Hyperfluorescence: pooling**

**Early and Late Defect**

Early AV phase showing early fluorescence from the area of detached RPE.

Late phase showing well-demarcated hyperfluorescent borders.

In Pigment Epithelial Detachment (PED), fluorescein flows freely through Bruch's membrane into the sub-RPE space.

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**Hyperfluorescence from staining**

**Late Defect**

Drusen PED allowing staining or pooling of fluorescein.

Early: drusen not very apparent

Late staining of drusen (more common in large drusen)

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To determine the type of hyperfluorescence, we must determine the time at which the hyperfluorescence appears.
Hyperfluorescence: staining of fibrous scar

Late defect

Fibrous scar (white lesions)

Most common location is subretinal

Early hypofluorescence from blockage

Late hyperfluorescence from staining of fibrous tissue

Hyperfluorescence

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Hyperfluorescence

Early Phase & Late Phase

Hyperfluorescence due to abnormal choroidal vessels from a choroidal hemangioma.

Early filling from tumor vessels.

Late leakage.

Widefield FA with Optos
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