Fluorescence Angiography: from skeptic to apologist

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apotologist
/əˈpæləjəst/
noun
a person who defends or supports something (such as a religion, cause, or organization) that is being criticized or attacked by other people
Synonyms: defender, supporter, upholder, advocate, proponent, exponent, propagandist, champion, campaigner

Merriam-Webster Dictionary
Disclosure

- Novadaq Technologies, Inc.
  - Speaker’s Bureau
  - Consultant
Goals and Objectives

• By the end of this presentation, attendees should be able to:
  – Describe the physiology of fluorescence angiography
  – Appreciate what the images can or cannot tell us
  – Develop strategies for incorporating fluorescence angiography into clinical practice
  – Understand why there is resistance to accepting this technology in clinical practice
Wound Healing Basics

- Wounds need oxygen to heal
- Blood carries oxygen to tissues
- Atherosclerotic disease reduces perfusion to wounds, decreasing tissue oxygen and slowing healing
Assessment of PAD

- Palpation of Pulses
- Handheld Doppler
- Ankle Brachial Index (ABI)
- Toe Brachial Index (TBI)
- Segmental Pressures with Plethysmography
- Arterial Duplex Ultrasonography
- Skin Perfusion Pressures (SPP)
- Pulse Volume Recordings (PVR)
- Transcutaneous Oxygen Measurement (TCOM)
- CT Angiography (CTA)
- Magnetic Resonance Angiography (MRA)
- Traditional Angiography

- Intravascular Ultrasound (IVUS)
- Fluorescence Angiography (ICGA)
Fluorescence Angiography

- Indocyanin Green (ICG) is a fluorescent dye that is injected via a peripheral IV
- ICG binds to plasma proteins and is confined to the intravascular space
- Hepatically metabolized with half-life of 3-4 minutes
- Only contraindication is iodine allergy
Fluorescence Angiography

- Near IR laser light is shined on the area of interest
- ICG fluoresces and is picked up by the camera
- Quantitative analysis can be done using calculations of Ingress and Egress of ICG
Fluorescence Angiography

- The only existing technology that allows direct visualization of the microvascular circulation
- Better than what the eye can see
Ingress Rate = \[ \frac{\Delta \text{Ingress}}{\Delta \text{time}} \]

Egress Rate = \[ \frac{\Delta \text{Egress}}{\Delta \text{time}} \]
Imaging Techniques

• Static imaging - camera is not moved during the entire study
  – Allows quantitative analysis
  – Allows comparisons between studies

• Dynamic imaging – camera is moved over the body
  – Allows viewing of multiple areas
  – Misses the ingress/egress phase of the study
  – Does not allow for quantitative analysis or comparisons
100,000 foot view

“ICG binds to the blood, and if there is blood flow, there will be ICG and the image will glow”

• Assumption
  – if there is good blood flow, there will be a glow on the screen
  – more glow equals more flow (ingress rate can be used to measure PAD)
100,000 foot view

• Problems
  – Dose of ICG dye affects image
  – Physiologic state of the limb affects image
  – Skin color affects intensity of image
  – We don’t have a good grasp yet on what the numbers tell us in a predictive manner
2.0 cc ICG

3.0 cc ICG
Standardize Dosing of ICG

• Should a standard dose be used for all patients regardless of their size?
  – If dose is changed between images, it is difficult to make comparisons
  – Operational issues with regard to number of doses per vial of ICG
Does ICGA correlate with ABI?

- 46 patients underwent 57 revascularization procedures (44 Endo, 11 Open and 2 Hybrid) for 48 lower limb wounds
- An ingress of 27.3 PxS and ingress rate of 1.1 PxS/sec corresponded to an ABI of 0.4
- Post-revascularization, 80% of patients had ingress $\geq$ 27.3 PxS, 85% had ingress rates $\geq$ 1.1 PxS/sec, and 100% of those with compressible ABIs had an ABI $\geq$ 0.4

Jonathan D. Braun, Pooja Rajguru, David G. Armstrong, Joseph L. Mills  Objective Indocyanine Green Angiographic Criteria Using Ingress and Ingress Rate to detect SVS Lower Extremity Threatened Limb Classification (WIfI) Grade 3 Ischemia (In Press)
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Parameters to predict CLI

- Twenty-one patients with PAD underwent revascularization procedures
- Pre- and Post-revascularization imaging was performed
- Metrics taken from the images were compared with ABI, TBI, TP
Figure 8. Indocyanine green angiographic test parameters were defined graphically: (A) $I_{max}$; (B) $T_{max}$; (C) $S$ = $I_{max}/T_{max}$; (D) $T_{f/2}$; (E) $P_{ROI}$. Note: $I_{max}$ = magnitude of intensity from ICG onset to maximum intensity; $T_{max}$ = time from ICG onset to maximum intensity; $S$ = slope of intensity increase from ICG onset to maximum intensity; $T_{f/2}$ = time elapsed from fluorescence onset to half the maximum intensity; $P_{ROI}$ = fluorescence intensity measured 30 seconds after the onset of fluorescence.

Figure 9. The settings of the regions of interest (ROIs). ROI 1: from the Chopart joint to the Lisfranc joint; ROI 2: at the metatarsal bones; ROI 3: at the distal region of the first metatarsal bone.
Parameters to predict CLI

- A value of $T_{1/2} > 20$ seconds for ROI 3 was significantly correlated with a toe pressure of $<50$ mmHg (sensitivity: 0.77, specificity: 0.80)
Data free zone

• Existing studies correlate ICGA metrics to existing standards

• No studies give any prediction as to whether a wound is going to heal
High Glow with Low Flow?

- Patients with severe PAD may have images that show enhancement of the foot.
- Patients are expecting little to no enhancement, but images still light up.
100,000 foot view

• Images of obvious areas of focal ischemia are very powerful for patient and clinician

• Insufficient explanation of what the images can or cannot tell the clinician

• Difficult to make an informed clinical decision for some images
1,000 foot view

• A new model for angiogenesis
• Deeper understanding of physiology of wound healing
• Incorporating ICGA into clinical practice
Normal Wound Healing

ANGIOGENESIS “ON”

VEssel NORMALIZATION

Source: Dr. W Li The Angiogenesis Foundation
Chronic Wound Healing

- **Baseline Vascularity**
- **Acute Injury**
- **Perimeter Angiogenesis**
- **Chronic Inflammation**

**Angiogenesis “On”**

**Persist Abnormally “Stuck”**

“Hyperfluorescence”

Source: Dr. W Li The Angiogenesis Foundation
Model of Angiogenesis, Hyperpermeability, and Resolution

Evans Blue Dye Injection

Ad-VEGF-A\textsuperscript{164}
ANGIOGENESIS INCREASES IN HEALING, THEN IS PRUNED TO PHYSIOLOGICAL BASELINE

“Return to normal” vascularity

“Hyperfluorescence”
Hyperfluorescence

- Explains the contradiction that one sees with a bright blush in a limb with known PAD
- Decrease in hyperfluorescence may correlate with decrease inflammation and improved tissue function
Incorporation of ICGA into Clinical Practice

• What can ICGA show us?
  – Microvascular perfusion
  – Response to intervention
  – Focal Hypoperfusion/Ischemia
  – Angiogenesis?
Does ICGA show angiogenesis?

A superficial understanding would predict that as tissue angiogenesis increases, luminescence increases.
Wound Microcirculation Monitoring

Angiogenesis increases in healing, then is pruned to physiological baseline.

“Hyperfluorescence”

“Return to normal” vascularity

Source: Dr. W Li The Angiogenesis Foundation
Enhancing Patient Selection

- Incorporation of ICGA into surgical practice
- Incorporation into lower extremity assessment
- Serial evaluations to determine clinical response to therapy
  - Where does a single measurement fall on the angiogenesis bell curve?
ICGA in Surgical Practice

- ICGA guided debridement of wounds
- ICGA guided surgical planning
Case Presentation: IB
1/13/15

- MRI of the lower leg
  - Superficial edema without evidence of abscess or sinus tract
  - Marrow signal is normal
  - No evidence of osteomyelitis
  - Severe posterior compartment atrophy

- Case discussed with radiologist
  - No evidence of any soft tissue necrosis of the anterior tibial muscle compartment
One week later
2/11/15

- Patient taken to the OR
- Call from surgeon: "The LUNA was right!"
- Extensive myonecrosis of the anterior tibial muscle compartment
- STSG applied because it had already been harvested
Back to the OR

- Patient referred back to surgeon with request that we do intra-operative LUNA
Surgeon says...

• “I’m impressed. I wasn’t sure what I was signing up for... I thought I was just being polite and showing professional courtesy, but this really made a difference”
ICGA and Hyperbaric Medicine

- The use of HBO in wound care has been increasing year after year
- ICGA has the potential to better inform the hyperbaric physician as to the progress of the patient
Oxygen and Wound Healing

- Oxygen plays a large role in wound healing. It is one of the most versatile and powerful agents available in the management of chronic wounds.
- All of the major components of wound healing, collagen formation, angiogenesis, epithelialization, and bacterial killing proceed in proportion to the amount of oxygen available.
Tissue $pO_2$ levels: overall picture

Improved Wound Healing

40mmHg

- 500mmHg: Max rate of PDGF production and up regulation of receptor sites.
- 300mmHg: Max rate of VEGF production.
- 250mmHg: Max rate of collagen production is at this level.
- 150mmHg: Leukocyte killing of infectious organisms peak at this level.
- 90mmHg: Zero infections in subcutaneous tissue above this level.

Minimum level for normal wound healing.

- 36mmHg: Minimum level for minimum PDGF production.
- 30mmHg: Minimum level for leukocytes to kill bacteria by oxidative burst.
- 20mmHg: Minimum level for cell division, collagen synthesize, and migration.
- 10mmHg: Max rate of VEGF production.
- 1-2 mmHg: Below this level the mitochondria can not function.

Slide Courtesy of Brad Bailey, MD
Hyperoxygenation

- Higher amounts of oxygen are dissolved in the body
- Hyperbaric oxygen therapy allows enough oxygen to be carried in the plasma to maintain tissue oxygenation in the absence of blood (ischemia)
Mechanisms of HBO$_2$

- Tissue oxygenation
- Stimulation of angiogenesis
- Reduction of edema
- Amelioration of ischemia-reperfusion injury
Cycling of Hyperoxic Stress

- HBO$_2$ resets the normoxic setpoint, leading to a positive stimulus for wound healing and angiogenesis
- Stepwise increase in normoxic tissue oxygenation
The \( pO_2 \) Wave

- Baseline tcp\( O_2 \) 25 mmHg
- Increased tissue \( pO_2 \) last 2-8 hrs
- After 16-20 treatments the base-line tcp\( O_2 \) level starts to move up.
- The base-line level will continue moving up to within 80% of normal tissue/post HBO.

- Level required for normal wound healing 40 mmHg
- Baseline tcp\( O_2 \) 25 mmHg
- 20 mmHg
- HBO Tx. 120 mins.
- Tissue \( pO_2 \) levels 2-6 hrs post therapy.
- Approximately 16-18 hrs until next treatment.

Slide Courtesy of Brad Bailey, MD
Growth of the Field
US HBO$_2$ centers

Courtesy of Tom Workman
Cost of Wound Care


Slide courtesy of Caroline Fife, MD
Patient Identification

- Hyperbaric patients should have:
  - Tissue hypoxia
  - Tissue hypoperfusion
Patient Selection

Patients who will heal without HBO₂

Patients who might heal with HBO₂

Patients who won’t heal even with HBO₂
Patient Selection

Patients who will heal without HBO₂

Patients who might heal with HBO₂

Patients who won’t heal even with HBO₂
Hyperbaric Patient Monitoring

• Has there been a response to therapy?
  – Is there angiogenesis?
  – Is there improved perfusion?
  – Is there improved oxygenation?
  – Is there a continued need for HBO\(_2\)?
When do you stop HBO$_2$?

- When the body is able to carry on the process of healing
  - Able to maintain tissue oxygenation
  - Able to maintain angiogenesis
  - Able to maintain tissue regeneration
Case Presentation: DA
Hospital Course

• Patient admitted for IV antibiotics
• Foot and Ankle surgery took patient for amputation of the great toe
• We requested that the LUNA be used intra-operatively
Intra-operative s/p disarticulation of great toe
Intra-operative s/p closure of skin flaps
Assessment and Plan

• Compromised Flap
  – ICGA identified area of focal ischemia
  – Surgical wound was compromised and had higher risk of healing failure
  – Hyperbaric oxygen therapy ordered
  – Room air TCOM on 1st webspace was 20 mmHg rising to over 600 mmHg at 2.4 ATA
Post-operative Day #28
Post-\( \text{HBO}_2 \) #16
When do you stop HBO$_2$?

• What are the parameters to determine when native tissue is competent?
  – Complete healing?
  – TCOM normalization?
  – Arbitrary number of treatments?
Wound Microcirculation Monitoring

Angiogenesis increases in healing, then is pruned to physiological baseline.

"Hyperfluorescence"

"Treat to normal" vascularity

Source: Dr. W Li The Angiogenesis Foundation
Post-operative Day #35
Post-HBO₂ #19
Intra-operative
s/p closure of skin flaps

Post-operative Day 3

Post-operative Day #28
Post-HBO₂ #16

Post-operative Day #35
Post-HBO₂ #19
What did ICGA answer?

- Was there an area of focal ischemia? YES
- Was there a clinical response to HBO$_2$? YES
- Was there a need for further HBO$_2$? NO
Case Presentation: RS
History

- 69 year-old gentleman
  - poorly controlled diabetes
  - atherosclerosis of the extremities
  - previous left transmetarsal amputation because of osteomyelitis of the foot
    - seen in our clinic in March 2013 and received a course of 50 hyperbaric oxygen treatments to save the left foot TMA that had dehisced
Clinic Course

- Podiatrist called and saw patient that afternoon for x-rays and labs
- CT Angiogram ordered as patient had pacemaker
  - No CTO but rather multiple areas of focal narrowing of the SFA, popliteal and peroneal branches
  - 3 vessel runoff visualized to bilateral feet
Clinic Course

- Patient sent to his interventional cardiologist for evaluation
- Plan was for angiography and percutaneous revascularization on 12/2/14
Post-Angioplasty

- Rotational atherectomy performed 12/2/14
- Peroneal artery was patent
- Posterior tibial artery was opened
- Anterior tibial artery was occluded, but revascularization was not attempted
  - Note was made that if the wound did not heal that a retrograde approach through the dorsalis pedal artery could be attempted
Assessment and Plan

- Acute Ischemia of a Wagner 4 DFU
  - Surgical Intervention
  - Revascularization
  - Adjunctive HBO$_2$ as temporizing measure to keep tissue viable while surgery and revascularization was planned
Clinic Course

• TCOM was 0 mmHg at the dorsal foot at sea level room air

• TCOM in chamber was 800 mmHg

• LUNA fluorescence angiography used to see what the perfusion looked like
Clinic Course

• **Limb salvage (TMA) vs. BKA**
  
  – Question as to whether patient would heal a TMA
    
    • Plantar arch patent
    
    • Dorsal arch ischemic
  
  – Progressive necrosis of toes
  
  – Podiatrist requested 2nd angioplasty with attempt to open the anterior tibial artery prior to attempting any surgery
  
  – 3 hour procedure with canalization of the dorsal arch, but unable to cross occlusion
  
  – Given lack of new blood flow, prediction of 20% chance of success
What did ICGA answer?

• Was there an area of focal ischemia? YES
• Was there a clinical response to HBO$_2$? NO
• Was there a need for further HBO$_2$? MAYBE
Case Presentation: KN
History

• 53 year old female with a history of chronic back pain and prior IVDA complains of fatigue and weakness around 1/14/15
• On 1/16/15 presented to the ER for evaluation but was discharged home
• On 1/17/15 she is found lying on the floor of her apartment, but did not want to come to hospital
• On 1/20/15 the patient was found by daughter in her apartment in the same position as she had left her 24 hours prior
History

- Patient was brought back to ER with weakness and new onset foot pain.
- Workup found evidence of septic emboli to the lungs (CT Scan) and MRSA bacteremia
- Transesophageal Echocardiogram showed mass on right ventricle free wall
- ABI was 1.06 on right and 1.05 on left
- Blistering, painful and dusky toes prompted limb preservation consultation
Physical Examination

• Patient with exquisitely tender feet
• Weakness of lower extremities
• Bullae on dorsum of feet
• Areas of dusky pinkness on toes
• No eschar or erythema noted
Decision Making

- Atypical appearance of septic emboli
  - Is there any evidence of ischemia?
  - Is there an indications for HBO$_2$?
Assessment and Plan

- Acute peripheral arterial insufficiency from septic embolization as evidenced by focal areas of ischemia using ICGA

- Immediate initiation of hyperbaric oxygen therapy @ 2.4 ATA × 90 min BID for 48 hours then daily afterwards
  - Temporizing measure to oxygenate ischemic tissue until recanalization or collateralization can occur
Clinical Course

- Patient received BID treatments on Friday and Saturday, then daily treatment on Sunday
  - Pain gradually decreased
  - Toes did not develop necrosis or eschar
  - Erythema receded after BID treatments
Clinical Course

- Patient developed pericardial tamponade and required pericardial window with three chest tubes
- Toes monitored while in the ICU, no worsening clinically
- Patient taken to OR for drainage of a cervical epidural abscess
- Question of whether to continue hyperbaric oxygen therapy when stable
Assessment and Plan

- Toes did not progress to infarction
- Pain in foot had decreased
- Areas of focal ischemia resolved on ICGA
- Hyperbaric oxygen therapy was discontinued
What did ICGA answer?

• Was there an area of focal ischemia? YES
• Was there a clinical response to HBO₂? YES
• Was there a need for further HBO₂? NO
Integrating ICGA into Hyperbaric Medicine

- Identify and document patients who have hypoperfusion or focal ischemia
- Monitor changes in perfusion
- Determine stopping point
Caveats

- Lack of ICG uptake is not necessarily a marker of ischemia or hypoperfusion
- Single measurement less useful than serial measurements
- Data free zone
Future Directions

- Systematic evaluation of the technology in multiple areas
- Standardization of testing and interpretation
- Collaborative interpretation of results amongst early adopters
Goals and Objectives

• By the end of this presentation, attendees should be able to:
  – Describe the physiology of fluorescence angiography
  – Appreciate what the images can or cannot tell us
  – Develop strategies for incorporating fluorescence angiography into clinical practice
  – Understand why there is resistance to accepting this technology in clinical practice
Questions?

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