Fluorescent angiography used as a tool to guide angiosome-directed endovascular therapy for diabetic foot ulcers

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ABSTRACT

Angiosome-directed endovascular therapy for the treatment of chronic limb-threatening ischemia (CLTI) remains controversial owing to the overlap of wound angiosomes. Angiographic grading of success has limitations and translesional pressure assessments are seldom performed in the infrapopliteal vessels. Objective criteria to determine revascularization success in tibiopedal vessels have not been well described. Quantifying perfusion to a wound bed after establishing direct or indirect (via collateral) flow after revascularization is an important component for treating CLTI patients yet is seldom performed. We report the use of fluorescent angiography to quantitatively examine perfusion of a diabetic foot ulcer before and after angiosome-directed endovascular therapy. (J Vasc Surg Cases and Innovative Techniques 2021;7:159-63.)

Keywords: Angiosome-directed endovascular therapy; Fluorescent angiography

Chronic limb-threatening ischemia (CLTI) represents the most advanced stage of peripheral vascular disease. It is associated with high rates of amputation and death at 1 year (30% and 25%, respectively).[1] Angiosome-directed endovascular therapy uses a concept that wound healing is optimized with direct revascularization of an artery supplying a target angiosome. However, angiosome-directed endovascular therapy for diabetic foot ulcer healing remains controversial. Opponents claim that indirect revascularization via collaterals has similar healing rates, although the amount of collateralization required remains subjective and ill-defined.[2] Diabetic patients often lack adequate collaterals owing to progressive diabetic microangiopathy and multivessel involvement. We report the use of fluorescent angiography (FA) to quantitatively examine perfusion of a diabetic foot ulcer before and after angiosome-directed endovascular therapy using a SPY (Stryker Corp., Kalamazoo, Mich) fluorescence imaging platform. The patient consented to the publication of case details and images.

CASE REPORT

A 52-year-old man presented to the emergency room with a few days' history of flu-like symptoms, hyperglycemia, and a painful, swollen left foot. The patient had a significant past medical history of uncontrolled type I diabetes (hemoglobin A1c of 10.8%), peripheral neuropathy, and tobacco use. On examination, the patient had no fever, normal vitals, and a body mass index of 22. The pulses on the contralateral foot were palpable and nonpalpable on the left foot with biphasic anterior tibial (AT) signal and no posterior tibial (PT) signal. The left medial foot had a malodorous wound with purulent drainage (Fig 1, *A*) (WIfI score of 232). Laboratories were significant for a white blood count of 15 $\times$ 1000/μL and a glucose level of 466. A preoperative foot radiograph demonstrated gas within the soft tissue and no obvious osteomyelitis (Fig 1, *B*). The patient was taken directly to the operating room for debridement of the infected foot ulcer. The dimensions of the wound were 10 $\times$ 4 $\times$ 1 cm after sharp debridement of skin, soft tissue, muscle, and tendon (Fig 1, *C*). The first metatarsal was not involved. The deep tissue culture yielded polymicrobial growth, which included *Streptococcus gallolyticus* and multiple anaerobic bacteria that were not speciated. Blood cultures drawn at admission grew *Prevotella bivia* and *Fusobacterium gonidaformans*. After successful drainage of the infection and debridement of nonviable tissue, vascular imaging was performed.

Computed tomography angiography demonstrated mild superficial femoral artery disease with one vessel runoff to the left foot via the AT artery. The PT had a short segment occlusion in its distal third with reconstitution at the ankle.

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Author conflict of interest: none.

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2468-4287

https://doi.org/10.1016/j.jvscit.2020.10.014

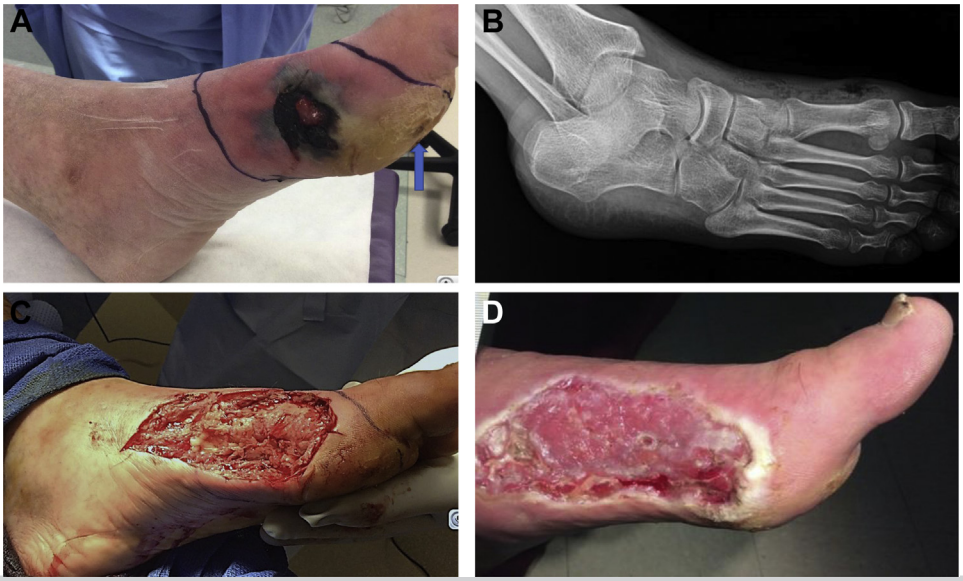

Fig 1. A, Preoperative image of left foot demonstrating complex diabetic soft tissue infection on the medial aspect with evidence of chronic callus (*blue arrow*) secondary to sensory neuropathy. **B,** Plain radiograph taken preoperatively demonstrating soft tissue emphysema and no obvious bony involvement. **C,** Intraoperative photo after debridement of skin, soft tissue, muscle, and tendon. **D,** Postoperative photo of nearly healed wound 4 to 6 weeks after initial debridement with interval skin grafting.

Transcutaneous oxygen pressure measurements were 48 mm Hg at the left calf and 10 mm Hg and 3 mm Hg at the ankle and foot, respectively. A transcutaneous oxygen pressure of less than 40 mm Hg is indicative of tissue hypoxia and inconsistent with wound healing.[3] After medical stabilization of the patient's organ dysfunction (renal and endocrine) and septicemia, the patient went to the angiography suite for endovascular angiosome-directed revascularization for limb salvage.

SPY FA of the left foot wound was performed initially and showed an ingress rate of 3.3 U/second (baseline) (Fig 2, *B*). After obtaining contralateral access, weight-based heparin was administered, and a selective left leg runoff was performed. Angiography demonstrated a chronic total occlusion in the mid to distal PT that filled distally by small, diseased collaterals off the AT (Fig 2, *A*). Successful recanalization of the PT was achieved using orbital atherectomy (a Diamondback 360 peripheral orbital atherectomy system, CSI, St. Paul, Minn) and gentle balloon angioplasty (Fig 3, *A*). SPY FA was then repeated. Quantitative analysis showed an increase from 3.3 U/second to 29.5 U/second, a total increase of 805% (Fig 3, *B*). Previous unseen fluorescence in the medial plantar (Fig 4, *A*) before the intervention was now easily visualized (Fig 4, *B*). Based on the intraprocedural SPY FA results, the procedure was terminated, and limb salvage was anticipated. The patient tolerated the procedure well and was discharged home. A successful, outpatient split-thickness skin graft was performed, and the wound was nearly healed at 1-month after revascularization (Fig 1, *D*).

DISCUSSION

Angiosome theory was first proposed by Taylor and Palmer in 1987,[4] who investigated blood supply to the skin and underlying tissues by ink injection studies, gross dissection, perforator mapping, and radiographic analyses of cadavers and isolated limbs. They defined angiosomes as a three-dimensional unit of skin and deep tissue supplied by source arteries and drained by source veins.[4] Their findings have been classified into six main foot angiosomes. Three of these are fed by the PT, one by the AT, and two by the peroneal artery.[5] Angiosome-directed endovascular therapy aims at recanalizing specific arteries that directly feed the wound or ulcer bed as compared with indirect revascularization, which relies on collateral flow from adjacent angiosomes.

The Global Vascular Guidelines recommend that angiosome-directed revascularization be considered in treating mid/hind foot lesions and lesions with advanced limb threat, because this practice seems to most notably improve wound healing.[6] Critics of angiosome-directed therapy claim foot wounds often have nebulous angiosome assignments, heterogeneous vascular anatomy, and frequently extend over multiple angiosomes.[7] However, for more proximal foot lesions, specific artery/angiosome assignment occurs in 75% to 80% of cases.[8]

Jongsma et al[9] found that direct revascularization showed similar long-term outcomes to patients who underwent indirect revascularization (with patent collaterals). In patients with diabetes, microangiopathy can negatively impact collateral circulation, complicating indirect revascularization. There is compelling evidence that direct revascularization using angiosome-directed endovascular therapy is superior to indirect

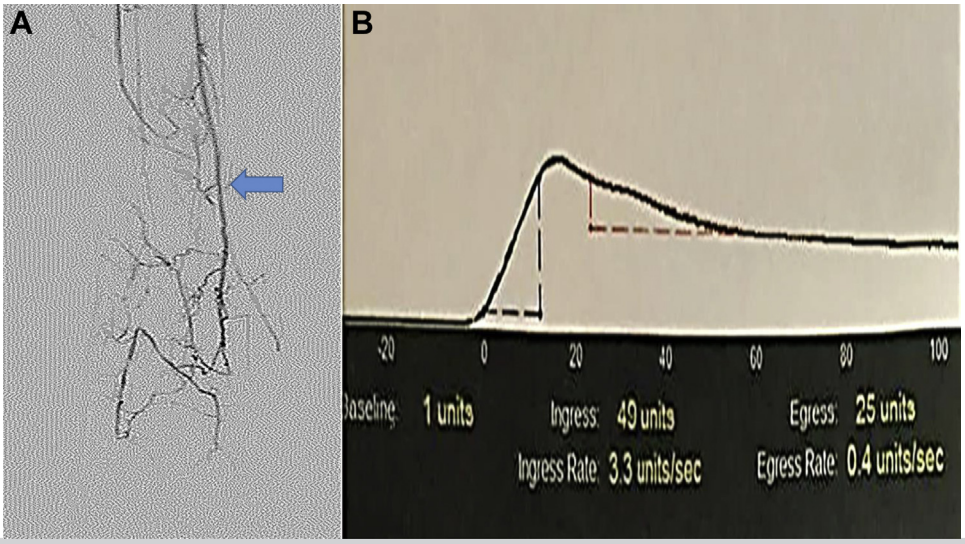

Fig 2. Preintervention. **A,** Digital subtraction angiogram image demonstrating continuous single vessel runoff (*blue arrow*) to the ankle via the anterior tibial (AT) artery. The posterior tibial (PT) artery occludes proximally and reconstitutes at the ankle via diseased AT collaterals. **B,** Fluorescence intensity curve demonstrating ingress, peak perfusion, and egress of tissue fluorescence before intervention.

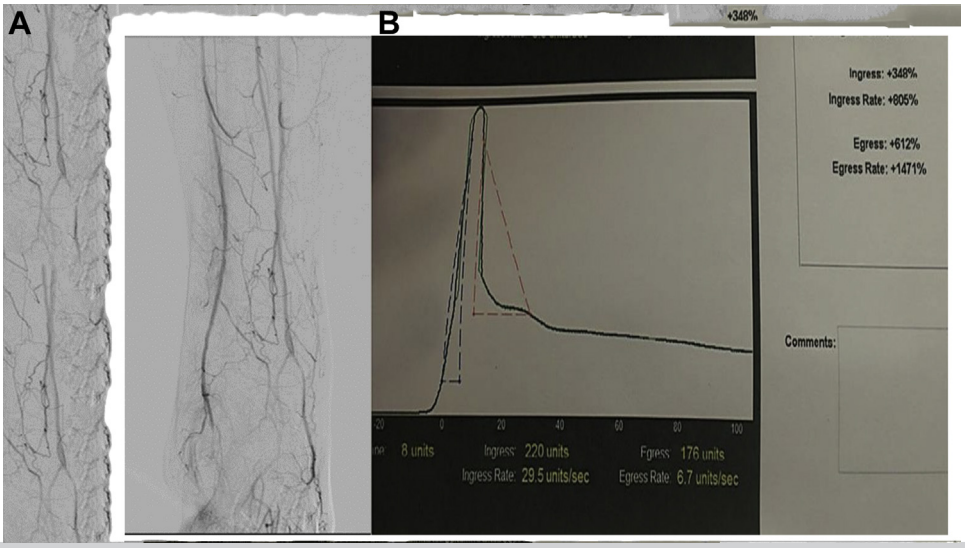

Fig 3. Postintervention. **A,** Digital subtraction angiogram image displaying recanalization of the posterior tibial (PT) artery after orbital arthrectomy and angioplasty. **B,** Fluorescence intensity curve revealing marked improvement in ingress rate, peak perfusion, and egress rate. Ingress rate is defined as the rate at which the fluorescence intensity increases in the wound bed. Peak perfusion is the change between the baseline and peak fluorescence. Egress rate is the rate at which the fluorescence diminishes and is more dependent on venous outflow.

revascularization in diabetic foot ulcers.[10] Proponents of this technique have documented improved wound healing rates and amputation-free survival in patients with diabetic foot ulcers.[10,11] Angiosome-directed therapy should be weighed based on ulcer location, crural arterial anatomy, and degree of collateralization.

Currently, there is no standard for intraoperative measurement of tissue perfusion. Indocyanine green (ICG) is a long-standing contrast agent that has been approved by the US Food and Drug Administration since 1959. It is an inert, water-soluble, nontoxic agent with a short half-life of 3 to 5 minutes, a very low rate of adverse effects, and hepatic clearance; as such, it is a viable option for patients with kidney disease.[12] ICG's brief half-life permits repeat assessments during the same procedure. A standard ICG dose of 3 mL of a 2.5 mg/mL solution is recommended by the manufacturer and followed by our practice for the evaluation of peripheral perfusion. The

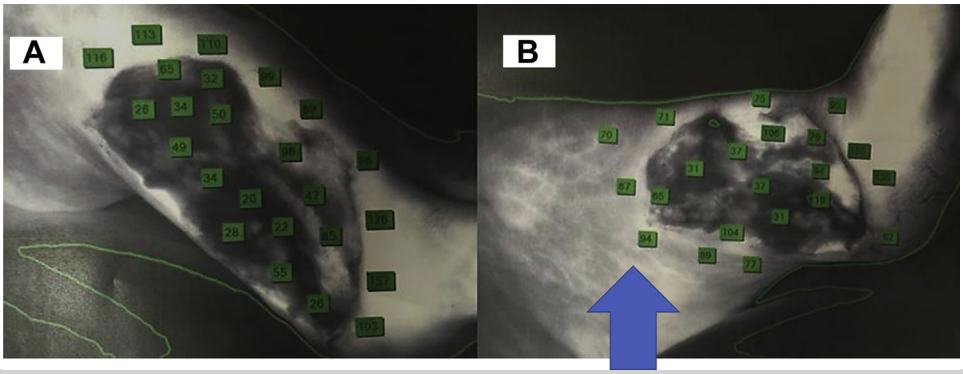

Fig 4. Fluorescence angiography representative images. The numbers in the *green boxes* represent absolute values of fluorescent activity based on a scale from 0 to 255. These numbers are unique to each patient and vary by local vascular perfusion, presence of nonviable tissue or inflammation, and degree of ambient light. The dark areas represent low indocyanine green (ICG) uptake, which can be influenced by local wound factors, such as devitalized tissue or poor perfusion compared with adjacent area. **A,** Preintervention grayscale wound image at maximal intensity and assigned ICG concentration in the tissue. **B,** Increased ICG uptake in the medial plantar image (*blue arrow*) postintervention representing improved wound perfusion.

SPY system contains a near-infrared laser light source and charge-coupled camera that detects local ICG fluorescent tissue perfusion. The SPY system has a versatile imaging head that holds the laser diode ray, charge-coupled camera, and distance sensor. The camera is then positioned based on the range bar shown on the monitor (Fig 5). It can illuminate a maximum field of 18.5 $\times$ 13.5 cm^2, with image sequences at 3.75 to 30.00 frames per second depending on recording time ranging from 30 seconds to 4.5 minutes.[13,14] From this, values such as ingress, ingress rate (rate at which fluorescence intensity increases on imaging field), peak perfusion (ie, maximum intensity), egress, and egress rate are quantitatively determined while simultaneously displaying qualitative visual results.

SPY using ICG has been adapted by many other surgical disciplines, but has yet to be widely used for limb salvage. Braun et al[15] showed statistically significant improvements in ingress, ingress rate, curve integral, end intensity, egress, and egress rate after revascularization treatment in patients with CLTI. In the largest prospective study assessing SPY technology in peripheral interventions to date, Colvard et al[16] showed statistically significant improvements in ingress rate and peak perfusion after revascularization procedures for CLTI. They argue FA may serve as a marker for procedural success especially in diabetic patients with noncompressible ankle-brachial indices (ABI) or unavailable toe pressure (TP) measurements owing to tissue loss or infection.

Limitations in the use of SPY FA include the costs associated with the product, variable insurance reimbursement, unestablished threshold values, limited tissue penetration of 5 mm, and a lack of beneficial effect in amputation rate reduction. FA has not been well-studied in the treatment of CLTI; however, it may prove useful in real-time decision making. SPY FA may have the potential to predict wound healing during angiosome-directed therapy. Further investigation on its role in the management of diabetic foot ulcers and limb salvage is warranted.

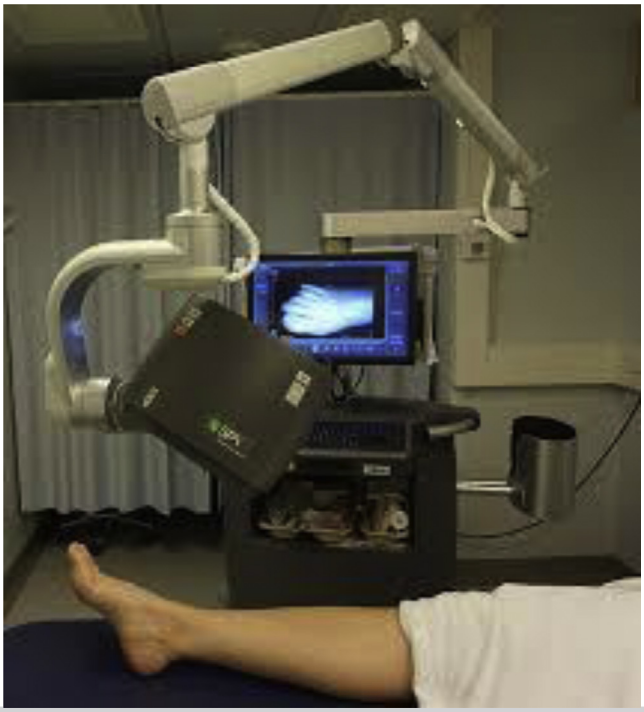

Fig 5. SPY Elite fluorescence imaging system with laser diode and display monitor allows surgeons to evaluate tissue perfusion in real-time without ionizing radiation.

Currently, there are no reported surveillance data in the literature supporting normal SPY values or threshold levels required for wound healing or relief of CLTI. The clinical interpretation of SPY values remains undefined given ICG variance among individuals and wound beds.

Settembre et al[17] evaluated the FA, ABI, and TP in 104 limbs before and after endovascular or open revascularization. An ABI could not be obtained in 57% owing to medial calcinosis and TPs in 48.5%, mostly owing to previous tissue loss. FA was technically successful in all limbs, and the SPY values failed to increase in 8.8% who underwent successful revascularization and none who failed revascularization.[17]

In this case, SPY FA provided intraprocedural information after recanalization of the PT with regard to the microperfusion of the wound bed. Wound ICG uptake was measured and compared with baseline values obtained prior to draping. Given the substantial visual and numerical intensity improvement of ICG, no attempt was made to restore flow to the dorsalis pedis and pedal arch. The marked improvement in SPY FA rate increase suggested limb salvage was probable, and it was reasonable to consider future split thickness skin grafting. The usefulness of SPY FA may be especially beneficial in cases in which in-line flow cannot be established. The added cost of SPY FA may be justified by its accurate assessment of tissue perfusion, ease of intraprocedural use to assist in real-time decision making, and cost reduction associated with avoiding unnecessary or futile limb salvage interventions.

CONCLUSIONS

SPY FA is a useful tool for evaluating perfusion and may guide the adequacy of endovascular interventions particularly in mid to hind foot lesions, and in cases where the affected angiosome has poorly developed collateral circulation. FA using ICG is a practical method of demonstrating perfusion before and after angiosome-directed endovascular therapy. It provides objective data in real time to assess if the intervention improved the microvascular perfusion of a wound which may be especially useful in cases where in-line flow could not be established. Further investigation in the use FA to direct angiosome-directed therapy is needed.

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Submitted Jul 30, 2020; accepted Oct 19, 2020.