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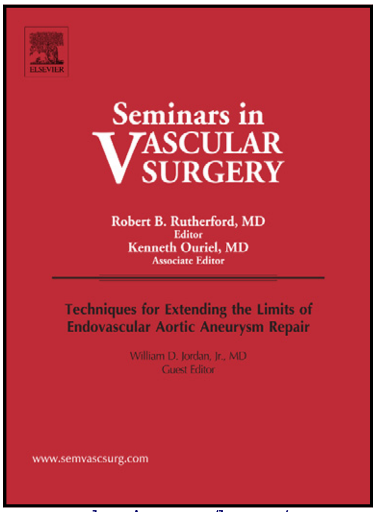

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PII: S0895-7967(15)00097-6
DOI: http://dx.doi.org/10.1053/j.semvascsurg.2015.12.002
Reference: YSVAS50488

To appear in: *Semin Vasc Surg*

The Use of Fluorescence Angiography System in Assessment of Lower Extremity Ulcers in Patients with Peripheral Arterial Disease: A Review and a Look Forward

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Keywords:

Fluorescence angiography, peripheral arterial disease, lower extremity ulcers, technological advance, wound care

Disclosures:

The authors have declared that no competing financial interest exists in connection with the authorship of this publication.

Abstract

The prevalence of chronic wounds is sharply rising throughout the world due to an aging population and increase in the incidence of obesity, diabetes and cardiovascular diseases. People with diabetes, hypertension and hyperlipidemia are at increased risk for developing peripheral arterial disease (PAD). PAD affects 8 to 12 million people over the age of 40 years in the United States and it is a major contributing factor in the development of lower extremity ulcers (LEU). While a number of non-invasive diagnostic tests are available to detect PAD in lower extremities, they have several clinical limitations.

In this review, current understanding of the pathophysiology of commonly seen LEU is described and vascular assessments typically used in practice are evaluated. Furthermore, the application of LUNA fluorescence angiography system (FAS) in screening and treatment of complex non-healing wounds in patients with PAD are discussed.

Introduction

An upward trend in the prevalence of obesity, diabetes and cardiovascular disease parallels the increase in chronic wounds. In the United States, chronic wounds afflict an estimated 6.5 million people.[1] The prevalence of chronic wounds, pressure ulcers, venous, arterial and diabetic wounds is expected to grow 7.6% by 2020.[2,3] Moreover, people with diabetes, hypertension and hyperlipidemia are at increased risk for developing peripheral arterial disease (PAD).[4] PAD affects 8 to 12 million people over the age of 40 years in the United States and it is a major contributing factor in the development of lower extremity ulcers (LEU).[5-7]

PAD develops as a result of atherosclerosis of the aorta, iliac and lower extremity arteries. In patients with poorly controlled blood glucose, hyperlipidemia and hypertension, endothelial cell dysfunction and smooth cell abnormalities may develop.[8] Structural changes in blood vessels can lead to inadequate blood supply to the tissues. Compromised peripheral blood supply leads to ischemia and hypoxia. Hyperglycemia is also associated with an increase in thromboxane A2, a vasoconstrictor and platelet aggregation agonist, which can increase the risk for blood clotting disorders.[9] Changes in extracellular matrix can also lead to stenosis of arterial lumen. [9] Moreover, presence of bacterial infection in LEU is well documented.[10,11] If left untreated, it can lead to serious complications for the patient. LEU pose a significant clinical and economic burden. It is not uncommon for wound care specialists to see patients who have suffered for years or faced amputation of the limb as their only option to alleviate the pain.

Early detection and ongoing monitoring of PAD is essential in effective management and prevention of complications such as ulcers, gangrene and amputation. While non-invasive vascular assessments offer clinicians a simple and cost-effective method to evaluate PAD, these tests have several clinical limitations and practical challenges. There continues to be a pressing need for a more efficient vascular screening tools that can aid treatment decisions in patient with LEU. LUNA Fluorescence Angiography System (FAS) (Novadaq, Bonita Springs, FL) offers wound care specialists a novel technology to document baseline tissue perfusion and validate or revise treatment by assessing perfusion after therapies such as vascular intervention, hyperbaric oxygen therapy (HBOT) and negative pressure wound therapy (NPWT).

In this review paper, the current understanding of the pathophysiology of commonly seen LEU is described and vascular examinations typically used in practice are evaluated. Furthermore, clinical application of LUNA FAS in screening and treatment of complex non-healing wounds in patients with PAD are discussed.

Pathophysiology of Lower Extremity Ulcers

LEU can have more than one etiology.[12-14] Most LEU are caused by venous disease.[12] Reflux is the most common underlying reason which results from dysfunction in venous return from: a) incompetent valves in the superficial, perforating or deep veins, b) outflow obstructions in the deep veins and/or c) calf muscle pump failure because of disease influencing lower limb mobility.

Second most common cause for LEU is arterial disease. PAD is a major contributor of arterial disease, which results in narrowing or blockage of the blood vessels in the legs. Atherosclerotic obstruction usually occurs in the iliac, femoropopliteal and the distal branches, i.e. peroneal and tibial arteries. Patients with PAD have heightened endothelial and platelet activation secondary to a prothrombotic state. Some risk factors for PAD include diabetes mellitus, elevated low-density lipoprotein, hypertension, elevated fibrinogen and advanced age.[15,16]

Vascular Assessments

Vascular assessment in patients with LEU may include palpation of femoral, popliteal, posterior tibial and dorsalis pedis pulses. The ankle-brachial index (ABI) is usually the most common test performed in the evaluation of patients with PAD. ABI is the ratio of blood pressure measured at the ankle to that measured at the arm. An ABI < 0.75 indicates that there is a high probability that arterial insufficiency is present (positive predictive value 95% in a general practice population). It should be noted that incompressible, calcified arteries, presence of kidney disease or advanced age can cause a falsely elevated ABI.[17-19] Further, 10% of the general population have a congenital absence of the dorsalis pedis or posterior tibial artery.[20] In a cross-sectional study which compared pulse oximetry and ABI in patients with type 2 diabetes, Paameswaran et al. noted that ABI only had a sensitivity of 63% (95% CI, 46%–77%) and a specificity of 97% (95% CI, 91%–99%).[21]

In clinical cases where ABI cannot be interpreted, toe brachial index (TBI) may be used. TBI is the ratio between toe pressure and the higher of the two brachial pressures. TBI is taken more distally in the lower limb thus there is a greater chance of arterial pressure changes caused by stenosis located below the knee in diabetic patients. [22] While TBI is more sensitive than ABI in diabetic patients, there is limited evidence on the validity of the assessment. Although several guidelines recommend a TBI <0.70 as a cutoff, it is not strictly evidence-based.[17-19,23-26] Clinical presentations such as skin ulcers, gangrene or prior digital amputation may preclude measurement of toe pressures.

Transcutaneous oxygen monitoring (TCOM) is another commonly used non-invasive vascular testing method. TCOM gives an indication of the amount of oxygen that has diffused from capillaries through the epidermis. TCOM is used for wound healing prediction, amputation level determination and qualification of HBOT. While TCOM is not affected by calcified leg arteries, it does have other physical limitations; the probe cannot be placed over the plantar foot because the thickness of skin does not allow for oxygen permeation and it cannot be used in patients with edema and inflammation.[27]

The Skin Perfusion Pressure (SPP) is the pressure required for restoring microcirculatory blood flow following the release of carefully controlled occlusion. It provides an indication of the status of the proximal arterial system. Measurement of SPP has been shown to be useful in the assessment of PAD and critical ischemia. [28-31] SPP is not affected by arterial wall calcification and can be measured in the limbs when patients present with skin lesions on toe or digital amputation precludes measurement of the toe pressure. One of the disadvantages of SPP is that the area measured must be able to fit a cuff and the blood flow occlusion can be painful.

Fluorescence Angiography System

LUNA is an emerging fluorescence angiography system that enables clinicians to distinguish between perfused and non-perfused tissue. The system uses an injectable dye, indocyanine green (ICG), which produces a fluorescence image showing blood flow in vessels and perfusion. The system offers the clinician full control of the imaging head and the system produces images immediately on a computer monitor, allowing visualization of real-time tissue perfusion. Being able to predict perfusion and viability of the tissue allows for more effective treatment strategies and wound healing outcomes. The application and effectiveness of LUNA FAS in vascular surgery and wound therapy has been documented in a number of studies.[32-39]

The ability to visualize perfusion in real-time and quantitate microcirculation enables clinicians to assess critical information to a degree that is just not available in other non-invasive vascular methods. It is important to note that non-invasive vascular studies may actually prompt a higher level of amputation. LUNA FAS can be especially beneficial in predicting the level of healing and preventing amputation. For example, consider a case of 71 old Caucasian male with a non-healing right foot wound (Figure 1) and a known history of PAD, diabetes and bilateral femoral-popliteal bypasses, who had been advised a below knee amputation by the referring surgeon. At Regional Medical Center, he was evaluated preoperatively with LUNA FAS. The assessment revealed hypoperfusion of the wound bed and periwound skin, and the hind foot showed adequate perfusion (Figure 2). It was determined that the patient would benefit from hyperbaric oxygen treatment and was advised to return to HBOT. At HBOT visit 45, patient was assessed again using the LUNA FAS. The wound had nearly healed and the patient was returning to mobility. Employing LUNA FAS was critical in determining the salvageability of the foot and preventing a below knee amputation.

In another diabetic patient, an 80 year old African American male with right great toe wound and known PAD (Figure 3), noninvasive studies (lower extremity arterial dopplers) had shown proximal occlusion of right superficial femoral artery and lower than normal flow in the posterior tibial, anterior tibial and popliteal arteries. The left common, profunda and superficial femoral arteries showed lower than normal flow in the posterior and anterior tibial arteries. The LUNA FAS assessment revealed evidence of good perfusion to the forefoot except the right great toe and the left had poor perfusion globally (Figure 4). LUNA FAS enabled the clinician to determine the need and level of amputation. The patient was admitted for right great toe amputation and right superficial femoral angioplasty with plans to address the left side subsequently.

LUNA FAS provides a new platform for clinicians to not only visualize blood flow, but to also assess the ability of the wound to heal. Thus, enabling clinicians to determine the need for amputation or further treatment options that may preserve a patient's limb. As seen in the clinical examples, this imaging modality can greatly aid clinicians in treatment decisions and improve healing outcomes.

Discussion

LUNA FAS is a novel imaging technology that offers physicians an efficient diagnostic tool for screening and treatment of LEU and other chronic non-healing wounds. The ICG dye utilized by LUNA FAS is metabolized exclusively via the liver and has a documented record of safe clinical use.[40] ICG is contraindicated in patients allergic to iodine.[40] An important feature of ICG is that it does not leak into extravascular space, allowing for multiple images in the same patient settings.[40]

LUNA FAS assessment enables clinicians to distinguish between perfused and non-perfused tissue and provides a more objective assessment of arterial and venous flow, and oxygen or perfusion gradient in the wound. Noninvasive vascular assessments such as ABI, TBI, TCOM and SPP have several clinical limitations and these examinations do not allow for visualization of blood flow through the vessels. LUNA FAS provides a superior point-based microvascular assessment and allows for a more interactive patient education experience.

Moreover, LUNA FAS may be especially beneficial for screening chronic wounds in patients who would benefit from HBOT. Currently, a multi-center trial evaluating the effectiveness of early or late HBOT in the treatment of diabetic foot ulcers (DFU) based on

LUNA FAS or wound area evaluation at 4 weeks after randomization is underway. Correlation of LUNA FAS parameters with treatment decision, efficacy of discriminating microvascular issues and improvement in wound healing will be assessed. It is hypothesized that LUNA can be utilized to determine which patients are responding to HBOT and should continue treatment, and identify patients who are not responding and should be started on an alternative therapeutic regimen. Further studies will add to the data establishing evidence of effectiveness of this emerging diagnostic imaging technology for screening and treatment of chronic non-healing wounds.

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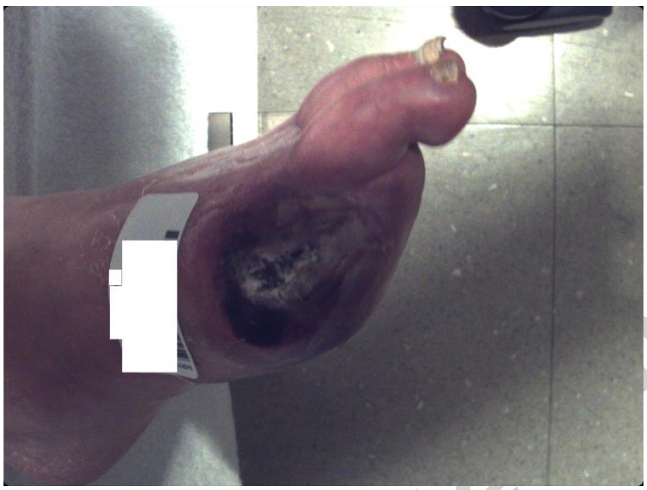

Figure 1: Non-healing right foot wound.

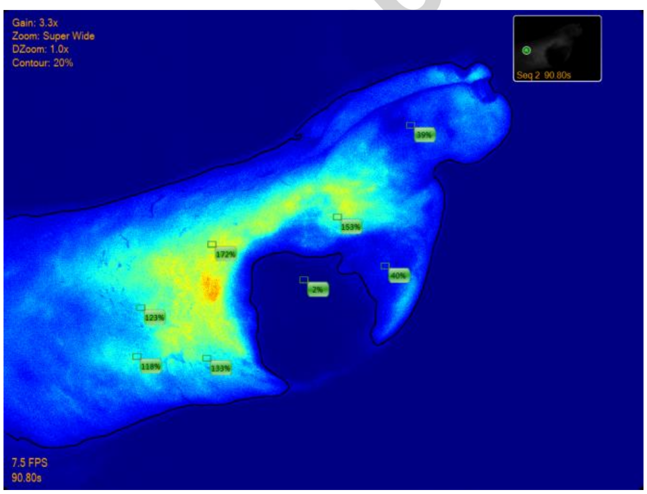

Figure 2: Hypofusion of wound bed and periwound skin

Figure 3: Right great toe wound with necrosis

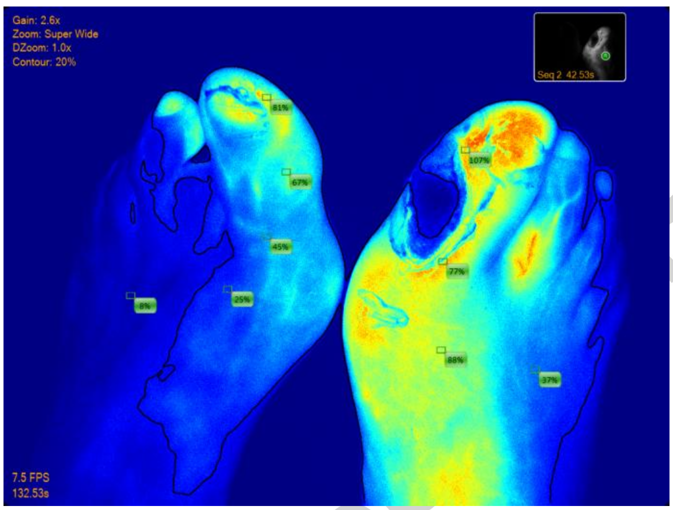

Figure 4: LUNA FAS perfusion assessment