Ischemic and Venous Wound Identification: What We Look For

Using macro- and microcirculatory characteristics, noninvasive and invasive tests, and available imaging to accurately diagnose and treat arterial and venous ulcers.

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Chronic leg ulcers affect approximately 1 million people in the United States, and this number likely rises every year.[1] The etiology of lower extremity wounds includes innumerable systemic diseases and concomitant risk factors (eg, infection, neuropathy, pressure, drugs) that clinicians should be aware of before considering treatment.[1] Although venous leg ulcers are the most common lower limb ulceration and represent 70% of all leg ulcers,[2,3] arterial (or ischemic) ulcers account for most severe tissue complications and potential limb loss.[1-3] Arterial ulcers are generally associated with macrocirculatory peripheral artery disease (PAD) and are detected in 18% to 29% of people aged ≥ 60 years.[4,5] An estimated 5 to 10 million people in the United States have PAD, and many are either underdiagnosed or may exhibit "silent" disease until complications such as leg ulcers appear.[1,4,5]

Patients with lower limb ischemic wounds have several risk factors that can increase the likelihood of severe tissue loss and major amputation, including increasing age, male sex, African American ethnicity, and the presence of peripheral neuropathy and/or infected ulcers.[6-8] In addition, the TASC II consensus statement noted that more than 15% of diabetic patients will develop a foot ulcer (all causes confounded) during their lifetime, and 14% to 24% of those patients will require amputation.[9] Tissue healing is complex and requires precise circumstances to unfold, free from regional hypoxic, inflammatory, neuropathic, or pressure conditions.[10] Combined with high-performance revascularization techniques that focus on "how" to rebuild arterial flow,[6-8,11,12] new strategies about "when" and "where" to plan appropriate arterial, venous, and foot wound therapy are emerging.[12,13]

CLINICAL CLUES AND MEDICAL HISTORY OF ULCERATION

Despite significant progress in research, the precise mechanisms that cause either ischemic or venous ulceration have not been completely defined.[3,6,10] However, several macro- and microcirculatory characteristics may aid in correct clinical assessment.[3-5]

Ischemic Ulcers

Ischemic ulcers are often described as "spontaneous" inferior limb ulcerations (typically located on the forefoot and toes) that occur when digital collateral flow progressively diminishes or arterial trunk occlusions develop.[13,14] Arterial ulcers can also appear as "post-minor traumatic" wounds (eg, common skin tears, cuts, blisters, abrasions, etc.) because local flow proves insufficient to increased oxygen demands for complete cicatrization.[14,15] Concomitant predisposing factors that facilitate ischemic tissue damage have been recently cited.[5-9] Bedridden status, tobacco use, dyslipidemia, uncontrolled hypertension, weight excess, hyperglycemia, uremic states, hypoalbuminemia, and hyperhomocysteinemia are associated with deleterious effects on normal tissue healing.[16,17] Other local, specific circumstances such as peripheral neuropathy, local inflammation, edema, regional infection, or abnormal pressure points are also threats to tissue recovery, beyond preexisting vascular impairment.[16,17] Although arterial ulcers can occur nearly anywhere on the ischemic limb,[16-18] coexisting multilevel arterial disease leads to more distal, localized ulcers, particularly in patients with deprived foot collateral reserves.[6-13] Arterial ulcers are often found on the distal leg, toes, forefoot, or around the heel (Figure 1), particularly in bedridden patients. Some arterial ulcers can imitate venous ulcers by having a perimalleolar local-

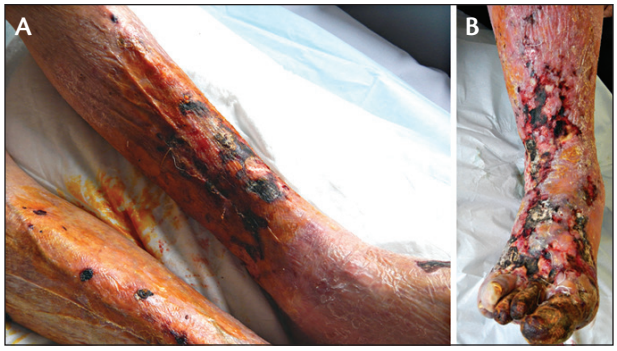

Figure 1. Different presentations of arterial ulcers (A, B). Beyond the characteristic features, the muscle's chronic hypotrophy, extended tissue necrosis, and the local septic spread suggest severe ischemia.

ization (Figure 2), and the differential diagnosis and treatment may not always be straightforward.[4,16-18] Ischemic ulcers often express characteristic pale-yellow purulent exudate with necrotic debris, alternating with gangrenous skin islands (Figure 1).[16,18] When areas of skin necrosis, deep fascia, or tendons are removed, there is no granulation tissue (Figure 3A). The boundaries of ischemic ulcers are marked by typical atone and poorly epithelialized tissue (Figures 1 and 2).[14-18] The presence of hypoxia (apart from parallel systemic factors) and uncontrolled hyperglycemia compromises infection control in normal tissues.[4,7,14] Not surprisingly, the majority of ulcers due to critical limb ischemia (CLI) and almost all neuroischemic diabetic foot wounds already have bacterial colonization at the time of referral.[15-18] Extensive skin necrotic changes often hide deep foot abscesses or eventual gangrenous zones, requiring urgent debridement and vascular referral.[16-18] Arterial ulcers are commonly accompanied by severe rest pain and hypoperfusion unless diabetic neuropathy coexists.[8] It is important to note that palpable distal pulses do not formally rule out underlying severe ischemic disease at the microcirculatory level.[13-15,18] Beyond common atherosclerotic ischemic ulcers, other "arterial-related" wounds can also be present such as the hypertensive ulcers, peripheral embolic tissue defects (caused by cholesterol particles of 0.01–0.2 mm in diameter), and wounds associated with different types of systemic arteritis, collagen diseases, or microangiopathic lesions.[3,10,14,18]

When local collateral reserve cannot compensate for the ischemia,[18,19] the readapting skin mechanisms are gradually exhausted, and tissue drifts toward biological decay.[18,19] The true "tipping point" between viable and nonviable foot structures likely relies on how well local collaterals and specific vessels can adapt.[18-20]

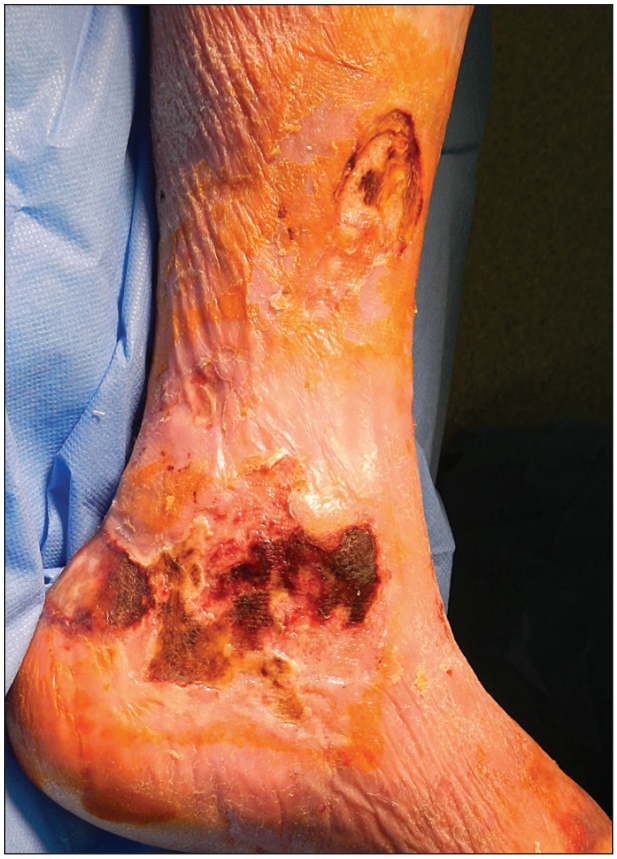

Figure 2. Ischemic wound located on the medial malleolar aspect of the leg, mimicking a "classic" venous ulceration.

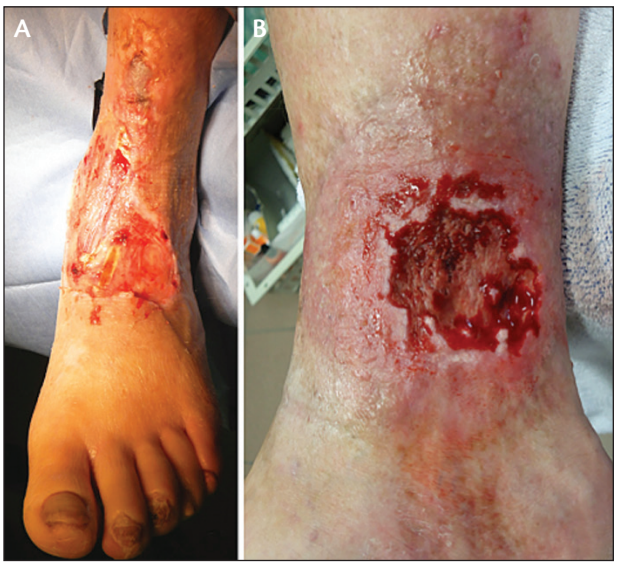

Figure 3. Arterial and venous ulcers after local debridement. Arterial ulcer: note the characteristic hypoxic, scarce bleeding, and atone tissue aspect after local debridement (A). Venous ulcer: note the specific granulation tissue and correct bleeding after necrotic tissue removal (B).

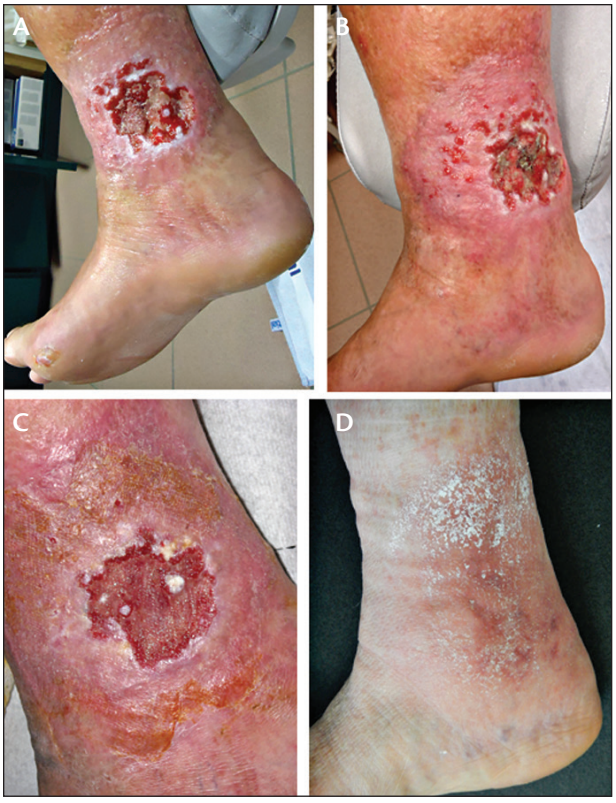

Figure 4. Venous ulcers. Distinct evolution from inflammatory (A) and exudative phases (B) to the granulation stage (C) and scar formation with chronic inflammation between ulcer relapses (D).

The timing and intensity of the main CLI threat, type of initial arterial pathology, remnant arterial trunks and branches, and promptness of debridement and revascularization all play decisive roles in any arterial ulcer assessment.[5,10,15-20] Although the onset of CLI may occur over days or weeks,[9] the local extent of infection and the number of collaterals lost to inflammation and septic thrombosis determine how fast tissue loss will occur.[19-21] Interventionists are often confronted with PAD patients who have more than one adverse factor for wound healing, which simultaneously interferes in physiologic cicatrization.[15,17,19,20]

Practical points. Arterial ulcers may mimic venous or neuropathic chronic wounds.[19-21] Thorough differential diagnosis is always required.[14-18] "True" arterial ulcers are relatively rare in the routine clinical practice. The informed clinician should always suspect other concomitant morbid conditions such as venous insufficiency or the neuropathic affectation, particularly in diabetic patients.[21] Perceptible distal pulses do not negate underlying severe ischemic disease at the microcirculatory level.[13-15,18]

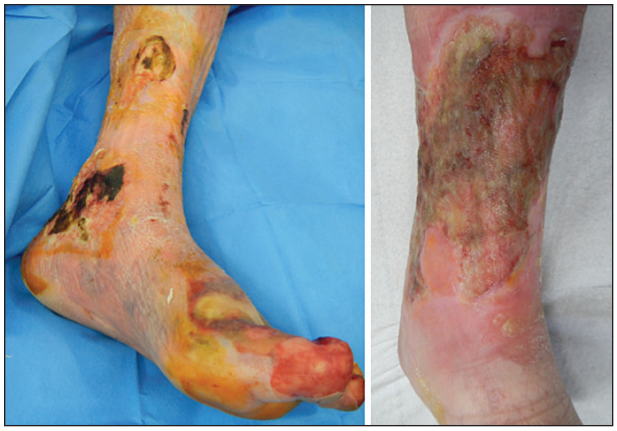

Figure 5. Mixed arteriovenous ulcerations.

Venous Ulcers

Venous ulcers are found in patients with prior longstanding chronic venous disease (Figure 4). In this context, orthostatic blood pressure in the deep venous limb system rises, enhancing venous hypertension.[1] This prime pathologic condition progresses from the perforator veins to the superficial venous system, leading to ongoing venular blood pooling and abnormal oxygen desaturation.[1-3] With venous valve failure, normal unidirectional flow (from the superficial to the deep system) is not present anymore, and valvular insufficiency leads to bidirectional flow.[1,14] Resistance to venous blood drainage creates chronic venous and capillary congestion, local inflammation, and edema, leading to progressive skin and underlying tissue changes (lipodermatosclerosis).[22] There is no consensus about the precise threshold from venous hypertension to venous ulceration.[1,22] Unlike arterial ulcers where ulceration and necrosis are often correlated with specific measurable thresholds (lower than 30–40 mm Hg evaluated by SPP or $TcPO_2$), for venous ulcers, there are no clear levels concerning the degree of blood pooling and abnormal local tissue oxygen desaturation that constantly mark the passage toward ulceration. Nearly 50% to 60% of patients exhibiting venous ulcers have incompetent superficial and perforator veins.[1] Approximately 25% of venous ulcers with confirmed venous pathology are associated with concomitant ischemic arterial disease (Figure 5).[23] Routine arterial monitoring is recommended for all perimalleolar chronic wounds.[1,22,23] If a mixed arteriovenous ulceration is diagnosed (Figure 5), classic compression therapy should be modified accordingly or omitted.[1,22,23] Modern recommendations in assessing venous ulceration indicate that both legs need to be inspected in the supine and erect position.[1,23]

Venous ulceration is commonly characterized by an irregular, well-defined border and a nonpainful tissue defect (Figures 4A–C).[3,23] However, deeper or mixed arte-

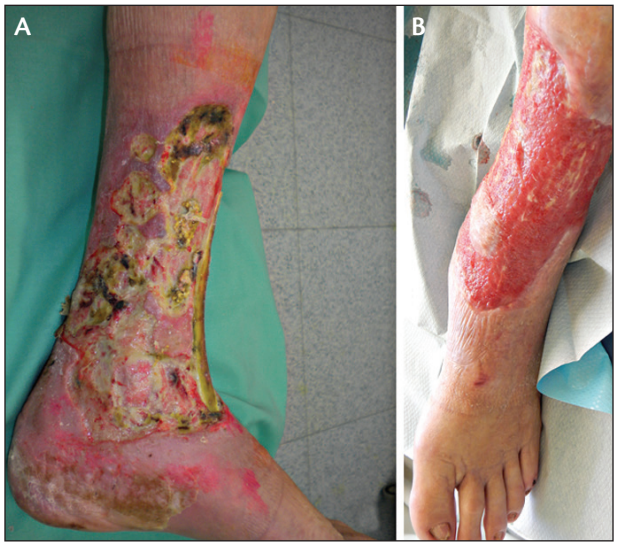

Figure 6. A more complex tissue defect in a diabetic patient with mixed arteriovenous and neuropathic ulceration. The initial presentation of CLI (A) and the clinical evolution at 7 weeks, owing to a multidisciplinary team approach (B).

riovenous ulcers can be highly painful (Figure 6).[22] Other venous characteristics include leg edema, varicose veins, local hemosiderosis, ankle flaring, local lipodermatosclerosis, or "atrophie blanche" (white atrophy) zones, and the presence of scar tissue from previous ulcers (Figures 4A–C and Figure 7).[1,3,22,23] The size and site of ulcers are variable, yet they are usually located at the internal aspect of the leg and around the medial malleolus (Figures 4 and 7).[22] The bed of these ulcerations often contains highly fibrinous exudates. Most venous wounds are infected at the time of examination and may then harbor purulent debris.[23] Unlike arterial ulcers, their base reveals normal and pink granulation tissue after debridement (Figure 3B).[3,23] Eczematous skin changes and venous dermatitis may also be present in the surrounding skin zones (Figures 4D and 7B).[1,23]

Venous ulcers and major clinical disabilities. Long-standing or underestimated venous disease can lead to irreversible skin and tissue deformities, affecting the patient's quality of life.[2,3,23] Relapsing wounds with vicious scars associated with the loss of subcutaneous fat and fibrotic skin changes can lead to an "inverted champagne-bottle" appearance of the leg.[1-3] This deformity causes difficulties in walking and standing, which greatly affects the patient's lifestyle.[23] The primary long-term complications of chronic venous ulcers are osteomyelitis and neoplastic transformation.[23-27] Long-lasting ulcers may require regular biopsy to rule out malignant changes.[24,26] If osteomyelitis is suspected, repeat biologic samples, plain radiographs, CT, MRI, and/or bone biopsies should be considered.[3,23,27]

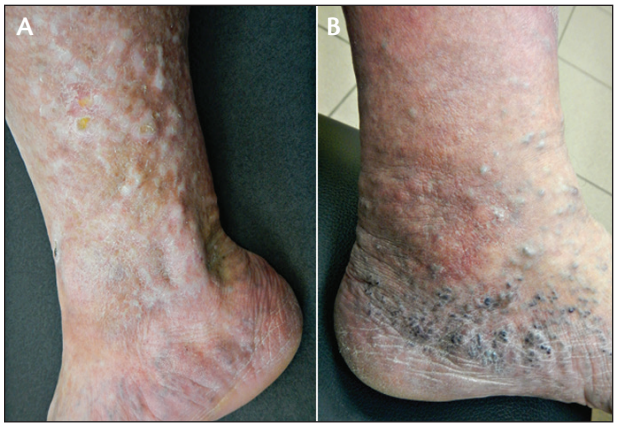

Figure 7. Venous ulcers with characteristic lipodermatosclerosis and ankle flaring.

Practical points. Every distal leg or foot ulcer should be initially suspected for concomitant ischemic disease, unless thorough clinical and noninvasive diagnostic testing proves the contrary.[22,23] In the absence of lipodermatosclerosis, venous origin of the ulcer should be questioned.[18,23] Nearly 25% of ulcers with a proven venous etiology are associated with arterial disease,[23] and more than 80% have other systemic risk factors.[24,27] If neglected, venous ulcers are not as innocent or harmful as previously thought (they can, however, lead to serious complications such as malignant transformation, osteomyelitis, septicemias, walking disabilities, etc). They require aggressive screening and treatment in the presence of concomitant venous disease or associated complications.[23]

DIFFERENTIAL DIAGNOSIS

Beyond dominant arterial, venous, or mixed arteriovenous etiologies, other conditions should be ruled out to correctly assess inferior limb ulcerations. Although rare, ulcers can also be caused by venous malformations (eg, Klippel-Trénaunay or Parkes-Weber syndrome)[23,24]; rheumatoid, hypertensive, or vasculitic diseases[23,27]; steroid, immunosuppressive, or sartane-linked medications[23,24]; nutritional, malignant, and contact dermatitis[23-27]; blood dyscrasia; and local infection (eg, as a result of trauma or neuropathy).[22-27]

NONINVASIVE DIAGNOSTIC TESTS

Several diagnostic methods may help the clinician better identify etiologic or parallel risk factors for inferior limb ulceration.

Arterial Ulcers

If the initial clinical diagnosis is unclear or the ulcer fails to show a clear trend toward tissue recovery, complementary arterial tests for PAD are recom-

TABLE 1. ARTERIAL TESTS FOR DIAGNOSING PAD

Ankle Pressure	Toe Pressure	Ankle-Brachial Index	Toe-Brachial Index	Transcutaneous Oxygen Pressure	Skin Perfusion Pressure
< 50 mm Hg	< 30 mm Hg	< 0.9/PAD	< 0.7/PAD	< 40 mm Hg	< 30 mm Hg
Expresses CLI	Expresses CLI	< 0.5/CLI	< 0.4/CLI	Impaired healing and presence of CLI	Impaired healing and presence of CLI

Abbreviations: CLI, critical limb ischemia; PAD, peripheral artery disease.

mended. The TASC II criteria[9] recognize the concomitant ischemic threat as the ankle pressure drops below 50 mm Hg or systolic toe pressure is lower than 30 to 40 mm Hg (Table 1.).[9] Ischemia is suggested by values lower than 50 mm Hg in diabetic patients.[9,17] Similarly, an ankle-brachial index (ABI) value lower than 0.5 (keeping in mind that ABI can be normal to high due to arterial wall calcifications),[12,17,20] or a toe-brachial index below 0.4 indicates an arterial problem.[9,17] Pulse volume recordings (a Doppler waveform study) and segmental limb pressure measurements (> 30 mm Hg decrease between two adjacent limb arterial levels) may also provide useful information on serial severe stenoses or occlusions in the main arterial trunk.[4-6] Doppler examination, when performed in specific topographic areas of the foot, may provide details on perfusion of the foot arches, remnant arterial collaterals, and flow orientation around the ischemic ulcer.[13,15] If routinely available, transcutaneous oxygen pressure and skin perfusion pressure techniques may provide helpful information on microcirculatory foot perfusion (Table 1).[9,13,17] Other noninvasive arterial examinations are duplex ultrasound and MRA,[9,13,17] which have a sensitivity of 94% and 98% and specificity of 94% and 91%, respectively.[4-6,15-17] Novel diagnostic modalities based on molecular scintigraphic imaging have been proposed for PAD and CLI management over the last decade. Molecular imaging can noninvasively visualize and score characteristic cellular ischemic changes in specific body sectors.[8,13,15] Positron emission tomography (PET) and single-photon emission CT (SPECT) use the ^{99m}Tc-sestamibi tracer to assess blood supply in the thigh and calf muscles in different atherosclerotic stages (Figure 8).[13,15] This method has been recently evaluated in CLI patients, with promising clinical results.[13,15] However, PET was superior to SPECT, with higher sensitivity and more stable attenuation in correction algorithms.[13] The main drawback of both PET and SPECT are image interferences due to local tissue inflammation and swelling.[13,15]

Venous Ulcers

Patients with chronic venous disease and venous ulcers should always undergo arterial assessment in parallel during their management.[22-24] Concomitant arterial disease requires simultaneous specific treatment, avoidance of certain treatments, or modification in venous compression therapy.[23,27] Chronic venous insufficiency requires noninvasive evaluation to ascertain between venous reflux or venous obstruction. The tourniquet test or early plethysmography assessment[22-24] have been gradually replaced by duplex ultrasound and the hand-held photoplethismographic devices. These diagnostic methods have a high sensitivity and specificity for detecting superficial and deep venous disease.[23,24,27] Duplex technology is used for precise, noninvasive assessment of venous reflux, for morphologic vein wall analysis, and when combined with proximal limb compression, it may assist the clinician in laser or surgical superficial vein ablation.[23,24]

INVASIVE DIAGNOSTIC TECHNIQUES

In cases where potential arterial disease has been suggested by clinical and noninvasive investigation, "invasive" imaging is recommended for planning a vascular intervention.[6-9]

Arterial Ulcers

Digital subtraction angiography (DSA) remains the gold standard imaging method for diagnosing below-the-knee arterial disease in CLI.[4-9] It is also an important clinical tool for wound-directed revascularization.[13,15,28-30] DSA provides the best spatial resolution for visualizing tibial and foot arteries in CLI assessment.[15-18] This information becomes essential in understanding each pattern of the vasculature and planning direct (wound-targeted) or indirect (collateral-supported) arterial revascularization.[13,15,28-30]

CTA is a diagnostic alternative to DSA given that new-generation multidetector CTA uses 64 channels or more.[6,31] However, CTA has diagnostic drawbacks related to exten-

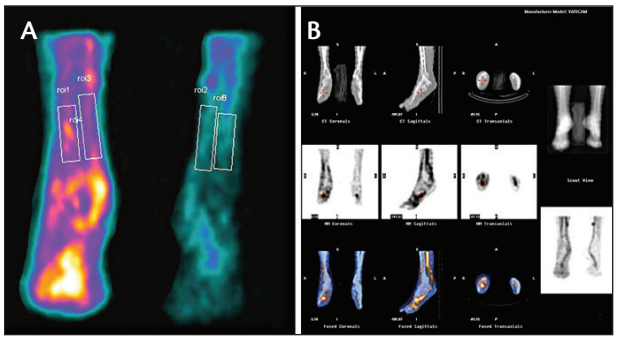

Figure 8. SPECT with bone scintigraphy using the ^{99m}Tc-sestamibi tracer showing the blood supply in the calf and foot muscles. Three-dimensional image with spacial resolution showing a normal (left limb, A) and ischemic (right limb, B) distal foot perfusion.

sive vessel calcifications or when detailed evaluation of foot collaterals is requested.[23,31]

Venous Wounds

Intravenous contrast phlebography is indicated in a limited number of cases.[23,27] Combined with venous CT (with image acquisition in the venous phase), both invasive techniques can confirm congenital venous affectations (eg, Klippel-Trénaunay or Parkes-Weber syndrome), can evaluate arteriovenous fistulas, and can be used in the workup of iliac vein compression syndrome (the May-Thurner syndrome).[24,27]

CONCLUSION

Accurate diagnosis of arterial, venous, or mixed leg ulcers is paramount for early treatment and optimal prognosis and is part of a larger integrated, multidisciplinary approach that supports new strategies for wound-directed revascularization, tissue regeneration, and limb salvage. Accurate arterial and venous flow evaluation beyond apparent diagnostic snares (some arterial, limb-threatening ulcers may mimic venous wounds and mislead physicians for prompt and aggressive "time-dependent" assessment and revascularization) offers correct etiological management, with undeniable serviceableness for patients (limb salvage). ■

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