Editorial

The 'Woundosome' Concept and Its Impact on Procedural Outcomes in patients with Chronic Limb Threatening Ischemia

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Clinical relevance:

This editorial assembles vascular and endovascular specialists from diverse clinical backgrounds and nationalities with a global call to address key challenges to enhance revascularization in Chronic Limb Threatening Ischemia (CLTI) patients.

- Dedicated below-the-ankle (BTA) angiography and revascularization is under-utilized in ischemic foot treatment. Existing guidelines don't address comprehensive BTA vessel analysis. CLTI trials also often lack data on in-line arterial flow to the ischaemic lesion and BTA vessel evaluation, hindering outcome assessment.
- Dedicated multi-planar angiographic evaluation of the distal microcirculation is key: direct arterial flow or good quality collaterals are crucial in influencing wound healing and need to be assessed diligently to the level of the distal ischaemic wound territory, termed "woundosome".
- An important primary emphasis of future trials should be on validating technologies and strategies for assessing tissue perfusion before, during, and after revascularization undertaken to heal tissue loss in CLTI patients. This will allow determination of a potentially significant delta in tissue perfusion prior to and following intervention at the "woundosome" level. Once changes in arterial perfusion have been identified as positively correlated to wound healing, these could serve as a much-needed novel primary technical outcome measure for patients with tissue loss undergoing either surgical, hybrid, or endovascular revascularization.

Background and current literature/guidelines

Chronic limb-threatening ischemia (CLTI) represents the most advanced stage of lower extremity peripheral artery disease (PAD) and is a major global health concern with escalating prevalence and significant healthcare costs [1]. Fortunately, technological advancements, evolving revascularization strategies, as well as refinement and expansion of the skill set of surgical and endovascular specialists have successfully reduced the number of patients previously deemed inappropriate for revascularization.

Despite mounting evidence on the value of BTA recanalization in wound-healing and limb salvage [2-5], the role of BTA angiographic evaluation and potential revascularization is yet to become the mainstay of ischaemic foot treatment in daily clinical practice.

The recent Global Vascular Guidelines on the management of CLTI [6] acknowledge limitations about incorporating the terminal circulation into its algorithmic framework. The concept of the preferred target artery pathway (TAP) does not include a comprehensive analysis of BTA anatomy, nor does it address specific mechanisms for establishing suitable perfusion to the ischaemic portion of the foot, whether through direct or indirect means. The TAP approach suggests that interventionalists should identify a preferred primary target path through the least diseased (or most suitable) crural artery, sharing some similarity with the surgical principle of bypassing to the highest quality vessel providing runoff to the foot. Additionally, the currently proposed pedal modifier, part of the Global Limb Anatomic Staging System (GLASS) classification [6], also has limitations in assessing the actual flow to the wound area. Nevertheless, it marks a significant step forward when compared to the most recent expansion of the Trans-Atlantic inter-Society Consensus (TASC) lesion classification [7], which did not include any assessment of BTA vessel status or account for the presence of multi-level occlusive disease.

Recent pivotal randomised controlled trials (RCTs) investigating CLTI treatments [8,9] were not designed to directly assess in-line arterial flow to the tissue loss territory during patient stratification, either before or after the index procedure. To illustrate, the Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-2 trial did not include data on the status of BTA arteries and foot arch patency [8]. The Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial group has to date reported infra-popliteal disease as a single “tibio-pedal” disease cohort [9]. While specifically designed to determine the best treatment for patients with CLTI, they did not provide explicit reports on angiographic data concerning pre- or post-interventional BTA artery status or the patency of the pedal arch. More specific analysis of each of the 21 anatomic segments, including the dorsalis pedis and pedal branches of the posterior tibial artery, and the association between anatomic patterns on presentation and clinical outcomes are eagerly awaited, with the hope that they will shed light on how in-line arterial flow to the wound was achieved and its potential impact on trial endpoints.

From the angiosome to the “woundosome”

In 2006, Attinger et al. [10] introduced the concept of six angiosomes in the foot and ankle, originating from the three main infra-popliteal arteries, as a dependable method to guide revascularization procedures and ensure direct blood flow to trophic lesions. However, doubts about the utility of the 'angiosome' concept have emerged over time. One significant limitation lies in its reliance on standard anatomy, disregarding potential anatomical variations, possible collateralized vessel contributions, such as from peroneal artery branches supplying anterior and/or posterior circulation patterns, and the role of a patent and non-significantly diseased pedal arch. Additionally, the frequent involvement of more than one angiosome in cases of larger wounds clouds its application. Consequently, despite two distinct meta-analyses indicating improved outcomes in terms of wound healing time and limb salvage for angiosome-targeted revascularization procedures [11, 12], this intriguing anatomy-based concept has not consistently translated into clinical effectiveness, as evidenced by various retrospective studies [13-18].

Existing literature focusing on CLTI patients with tissue loss has consistently indicated that the presence of direct arterial flow to the wound is associated with superior outcomes in terms of limb salvage and wound healing [19,20]. Conversely, the presence and quality of foot collaterals following indirect revascularization procedures have also shown to be important in predicting clinical success, often yielding results comparable to direct revascularization [21,22]. Unfortunately, recent reports frequently overlook the significance of true and choke collaterals, arterial connections, and the patency and quality of the foot arch when categorizing patients by disease severity.

Efforts have been made to develop various independent classification systems for BTA disease patterns. While the Kawarada pedal arch classification [23] is sometimes considered overly simplistic as it doesn't fully address the crucial aspect of peri-wound circulation, the specific classification of foot atherosclerotic disease originating from angiosomal source arteries by Alexandrescu et al. [24] offers a more precise framework for defining patterns of BTA disease. This recently published classification system represents a potentially excellent tool for studying the often-complex anatomy of the infra-malleolar circulation and its implications in foot perfusion, although its applicability and clinical significance remain to be validated in large-cohort studies.

Despite numerous attempts by previous authors to establish an acute performance measure, validation and consensus have remained elusive. The primary focus of revascularization efforts and consequently, the definition of technical success, should be centered on achieving a significant increase in arterial perfusion within the three-dimensional zone containing the ischaemic lesion. In this context, we propose the validation of the 'woundosome' concept. This area may extend beyond its angiosomal anatomical borders to encompass adjacent territories if connections are established by true and choke collaterals [25] and/or if the foot arch exhibits non-significant disease [26].

Assessing the Woundosome

To perform a comprehensive evaluation of the small-caliber below-the-knee outflow arteries, the preferred method is super-selective Digital Subtraction Angiography (DSA) via an antegrade ipsilateral femoral approach, with the catheter/sheath positioned just above the infrapopliteal trifurcation, as the CLI Global Society highlighted in their recent Expert Recommendation Statement [27]. Furthermore, to optimally visualize pedal arteries, an 0.018-inch or smaller wire compatible catheter should be placed as distally as possible in the tibial arteries and/or the infra-malleolar vessels.

Performing high-resolution intraoperative angiography from various views and projections is essential toward this objective. To improve angiographic visualization, local intra-arterial injection of vasodilators (such as nitrates, papaverine, or Calcium channel blockers) can be useful. These maneuvers allow operators to gain a comprehensive understanding of the feeding arteries to the wound bed, identify potential anatomical variations, pinpoint the specific territory requiring direct perfusion restoration, and assess collateral integrity, size, and flow.

Importantly, it is often necessary to conduct antero-posterior (dorso-plantar) and lateral angiograms of the foot to fully delineate perfusion to the ischemic penumbra [11]. Specifically, the former is crucial for revealing the source of flow for the metatarsal arteries and the specific woundosome from either below-the-knee (BTK) or BTA vessels. The importance of utilizing two orthogonal projections when examining the BTA vessels becomes particularly evident in cases involving an occluded foot arch (Fig. 1-4). For example, when dealing with a necrotic lesion of the first toe, a thorough examination of both the dorsalis pedis and medial plantar artery is imperative for identifying a suitable target for revascularization; while theoretically supplying flow to different angiosomes, both vessels have the potential to directly nourish the wound bed.

Although the benefits of in-line flow to the foot in patients with advanced tissue loss have been well-documented [2-5,19,20], the selection of patients for aggressive revascularization attempts should be grounded in the assessment of microcirculation functionality [28] and clinically validated radiological findings, such as the medial arterial calcification (MAC) score [29]. The simplicity and generalizability of this metric provides us with a predictive tool for assessing the potential success of limb salvage revascularization strategies. Its application has revealed that in patients with compromised or non-functional ultra-distal microcirculation, conventional open or endovascular techniques do not always sufficiently improve local tissue oxygen perfusion or attain limb salvage, even if infra-popliteal revascularization proves successful [28,29].

Recognizing patterns of advanced inframalleolar disease, which primarily affects the ultra-distal vessels, should prompt early referrals to centers experienced in alternative treatment modalities, such as deep vein arterialization (DVA). This is especially pertinent in cases where potential revascularization targets in the pedal vessels cannot be identified.

Current and emerging tools to evaluate foot perfusion

Over the past two decades, various techniques have emerged to evaluate the pre- and post-revascularization grade of ischemia in CLTI patients with tissue loss. Among these, the most utilized methods include Ankle-Brachial Pressure Index

(ABI), Toe-Brachial Pressure Index (TBI), Transcutaneous Oxygen Pressure (TcpCO2), Skin Perfusion Pressure (SPP), and Pulse Volume Recording (PVR) [12-13]. However, a significant gap remains in standardized methods for quantifying arterial perfusion at the wound bed, crucially intra-procedurally [30-32], and there is a growing awareness of the significant limitations of current assessment tools. The lack of reproducibility, standardization and predictive utility in current evaluation modalities also highlights the clear need for established perfusion thresholds that reliably correlate with short- and long-term hemodynamic and clinical success. This benefit of improved evaluation and prognostic instruments will likely be most pronounced in the presence of advanced ischemia and the most challenging wounds, where the risk of limb loss is highest. Anatomically, this may frequently be in cases where single-vessel peroneal runoff feeds the posterior and/or anterior circulation or when flow to the “woundosome” is solely provided by collaterals.

More recently, several potential on-table Clinical Objective Performance (COP) tools have undergone evaluation, including implantable micro-oxygen sensors, perfusion angiography, diffuse speckle contrast analysis, and pedal acceleration time (PAT) [33]. All of these offer promising prospects as adjunctive tools for objectively measuring foot perfusion at baseline, during revascularization, and post-procedurally, with the potential to standardize assessments of normal and abnormal foot perfusion. This standardization can significantly contribute to the establishment of arterial flow threshold targets customized for wound healing.

- Micro-oxygen sensors (Profusa Inc, San Francisco, CA). Preliminary data [34] suggests a unique role in evaluating the acute success of revascularization, including the assessment of autonomic system integrity. Moreover, mathematical calculations based on preliminary data from the OMNIA (Oxygen Monitoring Near Ischemic Areas) study show high sensitivity in predicting early success (or failure) of revascularisation efforts.

- Diffuse Speckle Contrast Analysis (PedraTech Pte, Singapore) is a novel monitoring system that measures perfusion through the application of up to 4 radiolucent pads to the peri-wound tissue. This device offers continuous, quantifiable evidence of tissue perfusion to a depth of 8mm by measuring the Blood Perfusion Index—a real-time indicator of blood cell movement in key microvascular spaces—both before, during, and after revascularization. Although the only available data, derived from a preclinical study, demonstrates the device's reliability and real-time responsiveness to changes in perfusion [35], more robust data on CLTI patients with tissue loss are eagerly anticipated.

- Perfusion angiography (Philips, Eindhoven, The Netherlands) studies the time-density curve of contrast volume flow in the foot based on a dedicated post-processing software algorithm. Despite being an interesting technology, it needs yet to achieve full standardization. Factors such as movement artifacts, the need for specialized machines and software, and a lack of clearly defined perfusion thresholds linked to wound healing or limb salvage have presented significant challenges [36].

- In contrast, the latest addition, PAT, has swiftly gained global acceptance due to its non-invasive, reproducible, objective, and user-friendly attributes, coupled with its proven reliability [37,38]. This innovative approach naturally aligns with the 'woundosome' concept. Within the intraoperative setting, PAT offers a definitive endpoint—a novel metric previously lacking—for decisively determining when sufficient perfusion has been attained during the procedure [33]. Currently, a multicentre study correlating PAT with Toe-Brachial Index (TBI), Ankle-Brachial Index (ABI), and arterial duplex has been completed and is awaiting final data analysis and publication [39]. The limitation of this technique relies on operator's ultrasound skills and the likely need for a dedicated specialized vascular technician in the room if the PAT needs to be measured intraoperatively.

Standardizing classifications

Initial assessment and stratification of CLTI patients using the WIfI (Wound, Ischemia, and foot Infection) classification has demonstrated the high predictive value of baseline WIfI classification and limb clinical stage in estimating the risk of amputation within one year [40,41]. The necessity for revascularization varies depending on the type of wound, its metabolic demands and the possibly concomitant need for different types of below-the-ankle amputation. The centerpiece of the current unmet need related to ischemic ulcerations of the toes, forefoot or heel is the lack of a clear understanding of the degree of perfusion required for successful healing, or any reliable, easy to use tool to assess perfusion changes. Deep or infected wounds may necessitate direct revascularization to facilitate this process, while superficial, non-infected wounds may not always require this intervention, important in the setting of challenging BTA disease [42].

Second-look procedures, often referred to as "redo-interventions," are often necessary to achieve durable resolution of presenting limb ischemia. As they reflect the recoil, restenotic and intimal hyperplastic forces that are not uncommon following endovascular or surgical revascularization, they do not necessarily represent initial treatment failure. These procedures frequently unveil previously unnoticed hibernating targets that have become visible and highlight areas where recently recanalized vessels may be recoiling. Similarly, a combination of rigorous surveillance and revascularization, guided by imaging and clinical findings, is essential until the wounds have completely healed.

Patients affected by CLTI should be managed by a dedicated interdisciplinary specialty care team, possibly embedded in multi-specialty driven “CLTI centers of excellence”, providing comprehensive imaging, clinical assessment, and treatment. In this setting, selective DSA should be considered the definitive ‘gold standard’ imaging modality, especially for distal occlusive disease associated with CLTI, as strongly indicated previously [27,43] but it could be augmented with intraprocedural perfusion monitoring.

Closing thoughts

We firmly advocate for the systematic inclusion of angiographic and physiological evaluations of BTA vessels, along with their tributary flow to the wound, as critical parameters in patient stratification criteria for forthcoming CLTI trials. However, it should also be recognised that angiography itself possesses a few limitations. It provides an only qualitative assessment of the distal vessels and requires subjective interpretation of the images, which in turn are affected by volume and flow rates of injected contrast. Flow improvement can only be assessed intermittently and requires boluses of contrast and radiation to do so. Finally, angiography only assesses visible vessels and not the extent or functionality of the microcirculation, where all actual oxygen and nutrient transfer takes place [30].

With ongoing evolution of multiple new perfusion measurement devices and techniques [44], the primary emphasis of future studies and trials should be on validating these technologies and strategies for assessing tissue perfusion before, during, and after revascularization. Once changes in arterial perfusion have been identified as positively correlated to wound healing, these could serve as a much-needed novel primary technical outcome measure for patients with tissue loss undergoing either surgical, hybrid, or endovascular revascularization.

Figures’ Legend:

Figure 1. A) 56-year-old man presenting with left diabetic foot attack, second toe necrosis and clear signs of local infection. B) Pictorial scheme of vascular duplex ultrasound highlighting triphasic signal in anterior tibial and peroneal arteries. The posterior tibial artery was found to be focally moderately stenotic but conserving strong pulsatile signals distally. C) Static wound with no signs of granulation at the level of the 2nd toe amputation site, despite best medical treatment and Vacuum Assisted Closure dressing applied.

Figure 2. Preoperative angiographic views of the ankle and foot. A and C) Latero-lateral projection. B and D) Antero-posterior projection. Dark purple dashed line:

anterior tibial artery and distally occluded dorsalis pedis artery (no connection with the deep plantar arch) and only lateral branches as ultra-distal outflow vessels; pink dashed line: posterior tibial artery; blue dashed line: medial plantar artery; dark yellow dashed line: threadlike collateral feeding the mid- lateral plantar artery; red dashed line: proximally occluded lateral plantar artery, providing flow to the deep plantar arch and to all the metatarsal arteries; light yellow dashed line (AP view): occluded segment of the lateral plantar artery where the yellow circle indicates the target area of the revascularization procedure on the lateral view.

Figure 3. Final angiographies after successful revascularization. A) Latero-lateral projection and B) antero-posterior projection highlighting the successful revascularization of the previously occluded lateral plantar artery (2mm angioplasty performed). Significant angiographic increase of blood perfusion at the level of the wound bed is noticed.

Figure 4. A-B-C) Gradual improvement with complete wound healing after 5 months

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