Singularities of the Pedal Circulation in CLTI: Time for Novel Merging Guidelines

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Abstract

Chronic limb-threatening ischemia (CLTI) is considered to be the most severe expression of lower-limb atherosclerotic arterial occlusive disease. Advanced stages of below-the-ankle (BTA) arterial lesions may have a notable impact on technical success of foot revascularization, on lower capacity of tissue regeneration, and on limb preservation. Although most recent studies focus on specific morphological (anatomical) information about peripheral arterial disease at the calf and foot level, a reunited angiographic classification that combines the pedal trunks (the foot arches) with large-to-small collateral disease is still lacking or remains poorly defined. Concomitant hemodynamic information about ischemic foot flow, which is subject to continuous pathophysiological variations, remains unknown. Unitary, standardized, and generally accepted quantitative calcium scoring and calcium indexation, specifically concerning the pedal arteries and foot collaterals, is also awaited. Levels of calcific burden in specific pedal arteries and foot-arch walls may provide useful information about local arterial stiffness, vascular resistance, and expectancy for patency, tissue regeneration, and foot preservation. These indicators may be usefully correlated in a new, reunited perspective gathering morphologic and hemodynamic evaluation in calf and foot territories, particularly in CLTI patients. It appears that novel guidelines may be needed to assess the ischemic pedal flow. These novel diagnostic scales should associate multilevel arterial branching disease classification, standardized calcification indexation, and commonly accepted hemodynamic foot-flow evaluation. Future studies are warranted to gain deeper understanding of these preliminary concepts, and the rationale for a wider diagnostic perspective in contemporary CLTI treatment.

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Chronic limb-threatening ischemia (CLTI) is considered a manifestation of lower-limb end-stage atherosclerotic occlusive disease. Distal foot reperfusion is technically challenging, and tissue regeneration capacity is diminished in patients with advanced grades of below-the-ankle (BTA) arterial lesions.[1,2] Such persistent anatomical and functional alterations may lead to unavoidable amputation despite sustained reperfusion efforts and occasionally "reinsuring" angiographic end-procedural results.[1-3] Most contemporary studies describe specific morphological (anatomical) information regarding direct or indirect revascularization of the tibial and main pedal arteries;[4] however, the status of the foot arches, the large arterial-arterial communicants, and angiographic features of large-to-small collaterals remain unclear or poorly defined in current classification systems.[3,4] Moreover, except for inframalleolar anatomical scoring systems that are currently available,[4] standardized information regarding the main functional variables that affect pedal arteries and collateral CLTI perfusion remains limited.[3,4] These additional hemodynamic data are important to complement current angiographic interpretation of the critically ischemic foot, which is subject to continuous arterial flow variations.[5]

CLTI interferes with native flow specificities (particularly in diabetic macro- and microangiopathy). Deeper understanding of perfusion in the critically ischemic foot allowed novel concepts such as the end-artery occlusive disease (EOAD)[3,5,6] or the neuropathic cutaneous steal-syndrome[3] to be described with notable clinical

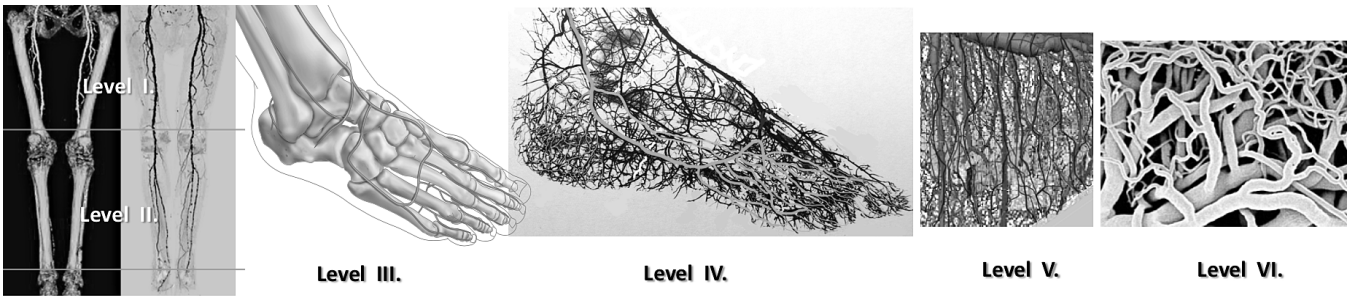

FIGURE 1. A succinct representation of main graded levels of arterial division in the inferior limb. There were described 6 levels of arterial degressive division starting from the macro, and down to the microcirculatory tissue perfusion. These levels can be summarized as Level I (femoropopliteal), Level II (the tibial trunks), Level III (gathering equivalent diameter pedal branches such as the angiosomal branches, the foot arches, the large arterial-arterial foot communicants, and large, 1-mm-diameter foot collaterals), level IV (the medium-to-small, <1-mm-diameter collaterals), and Levels V and VI (the microscopic arterioles and the capillary network). For every level of arterial bifurcation, the cumulated sectional area of the 2 distal ("secondary") branches proves to be superior to that of the genuine "primary" vessel.

usefulness to interventionists. The present article proposes an updated display of current apprehensions and interrogations about the pedal circulation in the CLTI environment.

Peculiarities of the pedal circulation. Similar to other regions of the human body, the pedal circulation is unique and can be described from both anatomical and functional perspectives. Owing to anatomical specificities, the arterial flow through this region is inherently exposed to continuous vulnerability to external mechanical forces and arterial turbulence. Additionally, this area is highly predisposed to sepsis, inflammatory edema, necrosis, scar formation, and bone deformation considering the risk of CLTI.[3] Pedal flow represents a specific zone in the human body where the main arterial axes act as "terminal territorial," or "end-artery disease branches."[5,6] This peculiar flow feature evokes lower collateral compensation capacity between specific foot regions inflicted by irregular collateral destruction during CLTI. However, all arterial territories of the foot do not offer scope for the development of collaterals to the same extent; for example, arterial collaterality may be natively poor, particularly in the heel and back foot, inducing a higher vulnerability to ischemia.[5,6]

From a physiological perspective, the pedal flow shows the highest vascular resistance in the inferior limb under normal conditions, which is worsened by CLTI, with a consequent variable but continued loss of collaterals.

Pedal circulation is referred to as a specific "lasting territory" owing to the lowest retrograde perfusion throughout the inferior limb.[5] It is difficult to standardize its current hemodynamic parameters considering the changes during walking, standing, and those consequent to local sepsis and inflammation, adding local neuropathic effects, among others.[3,5,6]

Accurate knowledge of the anatomical blueprint of the inframalleolar arterial branching pattern across several levels of distribution appears important to gain deeper understanding of the BTA flow characteristics.[6]

Arterial perfusion levels across the inferior limb. From a strictly anatomical point of view, the following 6 levels of arterial division (from macro- to microcirculatory tissue perfusion) are described in the inferior limb **(Figure 1)**:[6] Level I: femoropopliteal; Level II: the tibial trunks; Level III: pedal arteries and equivalent diameter branches such as the angiosomal branches, foot arches, large arterial-arterial foot communicants, and large foot collaterals (1 mm in diameter); Level IV: medium-to-small collaterals (<1 mm in diameter); and Levels V and VI: all microscopic arterioles and the capillary network.[6]

Notably, each anatomical level has a specific circulatory and hemodynamic role that cannot be innately compensated for; this finding is particularly relevant in the context of CLTI, which typically affects specific arterial trunks and their branches based on specific etiopathogenetic contributors.[5] CLTI affects not only this precise and balanced anatomical collateral network, but also the intimate functional and compensatory roles.

From a practical point of view, angiosome-directed revascularization essentially expresses topographic flow restoration via Level III (particularly the angiosomal branches and the foot arches), adding Level IV (the medium-to-small collaterals), and Level V (the arterioles). These levels participate simultaneously, however, with different impact in flow compensation and clinical results.[3]

Inframalleolar flow analysis should essentially include anatomical stratification that focuses on at least 2 division levels (Levels III and IV), adding accurate morphological calcium charge evaluation, and parallel functional flow appraisal. Comprehensive BTA flow assessment appears essential in this "terminal-type" perfusion territory,[5] using both anatomical and hemodynamic approaches.[5]

Currently available anatomical data. Rutherford et al[7] discussed the importance of thorough pedal atherosclerotic occlusive disease analysis in their pioneering work presented in the revised Society of Vascular Surgery (SVS) standards of treatment approximately 4 decades earlier.[7] The authors described

an initiatory foot run-off anatomical classification based on a simplified 3-degree (0-3, occluded, critically stenosed, or patent) severity score that specifically addressed pedal arterial disease.[7] The authors also proposed an original grading system for vascular foot resistance throughout the pedal arches from a parallel, integrated functional perspective.[7]

This anatomical and functional foot-flow evaluation model was accepted as the gold standard in clinical practice over more than 4 decades until the publication of the Global Vascular Guidelines (GVG), which recommended similar dual-infrainguinal assessment, and specifically for below-the-knee (BTK), and BTA run-off apprehension in CLTI.[4] Therefore, this first anatomical (angiographic) and hemodynamic flow stratification[7] remains relevant even in current CLTI research. Over the decades, several anatomical grading systems have endeavored to synthesize the main morphological features of BTA vascular anatomy in healthy individuals and in those with CLTI-induced pathology. Most studies have focused on atherosclerotic occlusive disease lesions detected and analyzed at isolated levels across the entire BTA arterial distribution (mainly the pedal trunks and foot arches).

Main pedal artery occlusive disease strictly restricted to the foot arches was predominantly analyzed and scored[8-10] using separate scales and various morphological grading systems.[8-12] These authors provided definite practical insights for BTA run-off and revascularization; however, they studied only 1 facet of the complex and multilevel anatomic scaffolding of the foot arteries from a single angle of analysis. Thorough preoperative anatomical evaluation is important and needs to include angiographic data about the integrity of the pedal trunks, pedal arches, main tarsal and metatarsal arterial-arterial communicants, and large arterial perforator connections (Level III branches).[3,6] Additionally, patency of the main medium-to-small territorial collaterals and detection of the deep plantar artery (an important connection between the dorsalis pedis artery and the plantar arch), together with the lateral and medial tarsal arteries evaluation (Level IV branches) should also be currently performed, particularly for planned wound-targeted revascularization (WTR).[6,9]

Baer-Bositis et al recently described an updated BTA run-off grading score for assembled pedal arteries and arches,[1] which may be useful to predict wound healing and limb salvage following endovascular therapy (EVT) for specific tibial revascularization. In a parallel specific surgical series, Rashid et al categorized the study group into those with complete, incomplete, and absent pedal arches[8] and observed that foot arch integrity significantly affected wound healing (independent of direct angiosomal revascularization) but did not affect amputation-free survival of patients.[8] In a comparable 3-variable study protocol using EVT in patients with diabetes, Troisi et al[10] observed that foot arch integrity was a singular significant anatomical predictor of tissue healing and limb salvage in patients with CLTI.[10] However, in a more detailed 4-variable study (type 1, 2A, 2 B, and 3) using the pure anatomical arch classification, Kawarada et al observed that severity of arch occlusive disease plays a key role in tissue healing in cases of CLTI, similar to the role of other statistically significant risk factors such as diabetes mellitus and foot infection.[11] The Global Limb Anatomical Staging System (GLASS) is a new anatomical staging system proposed by the GVG for infrainguinal arterial atherosclerotic disease.[4] The GLASS uses an inframalleolar 3-variable (P0, P1, and P2) run-off angiographic grading system to anatomically define the target artery path (TAP). Following previous SVS-documented standards of treatment,[7] the new GLASS classification is one of the few[4] to discuss the functional study of revascularization and additions of a new hemodynamic limb-based patency (LBP) parameter parallel to the TAP;[4] this avails a larger anatomical and functional modern perspective.[4]

All representative studies cited to date[1,7,8,11] except one[4] have focused on sole anatomical (morphological) analysis of pedal arterial disease, which is currently perceived at a single level of arterial division at the time. Currently, an exhaustive stratification of BTA arterial disease that includes all 3 aforementioned levels of arterial branching (Levels III–V) in unanimously accepted standards of evaluation is still unavailable.

Nevertheless, contemporary clinical research attempted to overcome this limitation. In a recent large cohort study that included 580 surgical and endovascular angiosome-oriented revascularizations, Settembre et al[12] observed, similar to the findings of other studies,[3,8,10] that pedal arch integrity (Level III) significantly affected wound healing and limb salvage and was additionally associated with successful angiosome-targeted revascularization, which is in contrast to several analogous previous remarks.[8,10]

In a recent single-center retrospective endovascular study, Bekeny et al[13] investigated the role of large-diameter arterial-arterial and collateral interangiosomal connections in 106 ischemic inferior limb wounds in patients with isolated infrapopliteal disease.[13] The authors observed 80%, 92%, and 63% wound healing rates associated with direct, indirect collateral-based, and totally indirect revascularization, respectively.[13] Based on their findings, the authors emphasize the superiority of indirect collateral-based revascularization (Levels III-IV) over single-source artery (isolated Level III angiosomal branches) targeted revascularization.[13] In their strictly anatomical study, the authors postulate that increased blood flow via topographically oriented collaterals (ranging from large-to-small, Levels III-V) oriented to specific foot ischemic zones may enable better blood flow for tissue healing compared with specific angiosomal source artery directed flow.[13] However, there are still limited references to the role of functional angiosome connections, main source artery specificities and scoring, and functional collateral flow contribution in the research.

Whether all surviving collaterals in specific regions of the CLTI-affected foot (with and without connections to topographic source arteries) are associated with comparable flow rates,

TABLE 1. Characteristics of below-the-ankle grades of arterial occlusive disease.

Foot Features	Grade A	Grade B	Grade C	Grade D
Foot TAAP	focal occlusions (<2 cm)	short occlusion ±2 cm (or <1/3 TAAP length)	occlusions >2 cm (or 1/3-2/3 TAAP length)	subtotal (>2/3) or total TAAP occlusions
Foot LFA	short occlusions (±2 cm)	short occlusion ±2 cm (or <2/3 LFA length)	occlusions >2 cm (or ± 2/3 LFA length)	subtotal (>2/3) or total LFA occlusions
Large collaterals (1 mm)	patent or short occlusions (<1 cm)	visible	severely deprived or absent	absent
Medium-to-small collaterals (<1 mm)	visible	visible	scattered patterns	severely deprived or absent
Calcifications	<50% of CTO length	<50% of CTO length	±50% of CTO length	>50% of CTO length
Associated tibial GLASS grades	3	3-4	3-4	4
Detectable limits of foot physiological AG	accessible	poor	absent	absent
Dominant number of involved for AG	1 angiosome	2 angiosomes	3 angiosomes	>3 angiosomes
Transcutaneous oximetry	accessible 50-60 mm Hg	generally accessible 40-50 mm Hg	mitigated accessibility 30-40 mm Hg	difficult to apply or inaccessible
Wounds: UT classification	dominant: solitary Grade 1, Stage D	dominant: often twin Grade 1-2, Stage D	multiple Grades 2-3, Stage D	foot/generalized Grades 3, Stage D

TAAP = target angiosome artey path; LFA = linked foot arches; AG = angiosome(s).

regenerative capacity, peripheral resistance (PR), and oxygen delivery uptake to the affected ischemic tissues still remains unclear.[3,5,6,14] A novel qualitative and quantitative collateral scoring system (considering individual foot collateral indices [CIs]) may be needed for effective WTR.[14] It is undeniable that Bekeny et al sustained a novel multilevel BTA atherosclerotic disease comprehension during the period when only single-rank arterial branch classifications (pedal trunks, foot arches, etc) were available. This type of standardized multilevel collateral stratification (which is currently unavailable) may be useful in the future for exhaustive morphological and hemodynamic evaluations of each individual CLTI presentation.[14]

Ferraresi et al[15] described an updated pedal arterial disease classification to categorize medial arterial sclerosis and calcification (MAC) as small artery disease (SAD) at the foot level.[15] Based on a retrospective study of 259 limbs, the authors observed that MAC and SAD could be considered anatomical manifestations of the same BTA occlusive disease, which can strongly affect the prognosis of major adverse limb events and limb loss in patients with CLTI.[15]

Considering these latest observations, a recent study performed by our interventional team proposed a novel morphological stratification of BTA arterial occlusive disease that focuses on specific atherosclerotic features involving 3 arterial levels in the foot (Levels III-V).[16] This expanded evaluation tool includes the main pedal arteries, the foot arches together with equivalent caliber arterial-arterial communicants, large collaterals (1 mm in diameter), and medium-to-small collaterals (<1 mm in diameter) in a reunited anatomical perspective of study.[16]

This classification globally follows the GLASS model using a selected infragenicular TAP pattern of atherosclerotic occlusive disease as a reference. This stratification exclusively focuses on pedal artery and division branches ischemic disease.[16]

Based on severity, 4 classes of targeted angiosomal artery path (TAAP) or pedal trunks disease are described and associated to 4 distinct classes of linked foot arches (LFA) disease and to specific lesions of large-to-small foot collaterals (**Table 1**) for each inframalleolar angiographic pattern. Combination of the 4 TAAP classes with the 4 parallel LFA and collateral classes led to the establishment of 4 novel anatomical grades (A-D) of pedal occlusive disease (**Figure 2** and **Table 1**). Limb salvage has been compared between patients with and without diabetes and also between grades A, B vs C, D in CLTI-affected feet.[16]

Based on a primary EVT approach, limb preservation of grades A vs C and A vs D was statistically significant (P=.04 and P=.03). Further comparison between grades A, B vs C, D proved ponderous for diabetics and non-diabetics (P<.001). The results of this study offer a model for comparison and grading of BTA occlusive disease at larger (3-branching level) assessment. It includes a wider stratification of synchronous macro, and microvascular disease in the CLTI foot. Similar to other associated contemporary articles,[12-15] this study confirms the importance of small-artery disease[15] and the MAC at the foot level,[15,17,18] particularly in diabetic patients.

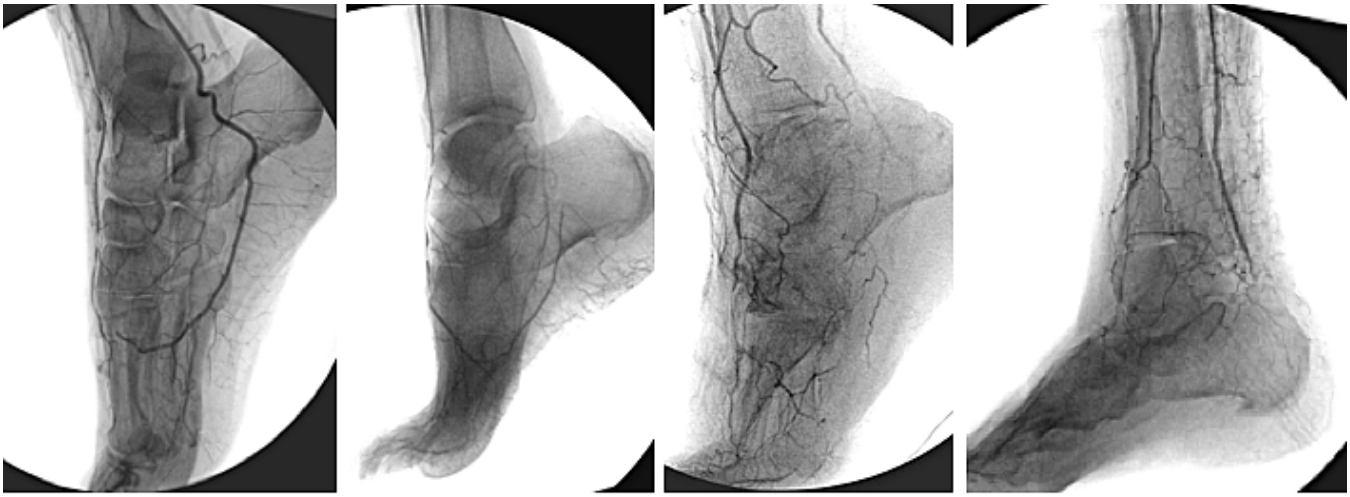

FIGURE 2. The 4 anatomic (angiographic) grades of inframalleolar arterial atherosclerotic occlusive disease. By assembling the 4 targeted angiosomal artery path (TAAP) classes of atherosclerotic disease with 4 other parallel linked foot arches and collaterals classes, 4 novel anatomical Grades A-D of pedal artery occlusive disease are illustrated by taking in this example the dorsalis pedis artery as the referent TAAP vessel.

Role of calcification in current anatomical evaluation of BTA occlusive disease. Severe inframalleolar atherosclerotic disease develops in parallel with expanding BTK arterial calcifications and represents 2 distinct facets of the same chronic and complex pathogenetic vascular phenomenon (which, however, remains partially understood).[17,18] Recent studies have reported a significant association between vascular calcification and increased cardiac and peripheral vascular morbidity and mortality[17-19] and a high risk of impaired wound healing and inferior limb amputation.[17]

Global research has described dystrophic or inflammatory (Type I) calcifications of the arterial intima, which are mainly dependent upon current cardiovascular risk factors and should be distinguished from metabolic or metastatic (Type II) calcifications at the arterial medial level, closely associated with calcium metabolism.[18,19]

MAC was mainly detected in patients with diabetes and renal disease.[17-19] The latest research has introduced a third category referred to as mixed calcifications, which is based on the association between previously described Type I + II categories.[19]

In a recent review, Lanzer et al[18] characterized MAC as a "systemic vascular disorder distinct from atherosclerosis that results in progressive calcification of the medial layer of the arterial walls."[18] MAC at the BTA level equally affects the pedal arteries, the foot arches, and the large-to-small foot collaterals; medial calcification is frequently associated with evolving stages of fibrotic-to-sclerotic medial artery thickening in medium-to-small arterial collaterals (diameter <1 mm) and may extend down to the arteriolar level.[15,16,18,19] More specifically, characteristic MAC in the pedal trunks and foot arches (Level III) is currently associated with medial sclerosis of small collaterals (Level IV) and arterioles (Level V), particularly in diabetic neuro-ischemic limbs and in renal patients.[20-22] The same study by Lanzer[18] proposed an original classification of MAC involving Stages I to IV (granular, confluent, circumferential, and extensive presentations). The more complex nodular calcification adding extreme arterial bone ossification is correlated with worse clinical outcome.[18]

MAC represents an independent and significant predictor of major adverse cardiovascular events, recurrent coronary incidents, the risk of prolonged dialysis,[18] high prevalence of BTK and BTA occlusive disease and CLTI,[19] and poor clinical outcomes associated with ischemic ulcer healing and limb preservation.[15-19] MAC of tibial and pedal arteries is significantly associated with type 2 diabetes mellitus,[15-19] particularly in patients with inferior limb severe diabetic peripheral neuropathy (DPN).[20,21] Despite a significant clinical correlation observed between MAC and DPN, the exact mechanism underlying this association remains unclear.[20,21]

Researchers have attempted to determine a scoring system for lower-limb calcifications and the clinical implications. Several stratification systems have been proposed over the last decade, and these are based mainly on angiographic findings and quantitative vs qualitative information. Liu et al performed a conspicuous retrospective calcium-quantitative analysis of data obtained from 250 patients.[22] They used a simplified inframalleolar calcific scoring system based on findings of plain foot radiographs (showing a minimum of 2 views). Scores range between 0 and 5, with 1 point each for calcification >2 cm in the dorsalis pedis, plantar, and metatarsal arteries and >1 cm in the hallux and non-hallux digital arteries.[22] The authors observed that a high MAC score was significantly associated with an increased risk of major amputation.[22]

Multiple regression analysis confirmed that the MAC score, diabetes, end-stage renal disease, and the Wound, Ischemia, and foot Infection classification (WIfI)[4] were significantly associated with high amputation rates.[22]

A recent quantitative classification proposed by Tokuda et al[23] uses a computed tomography scan-documented calcium score to assess femoropopliteal diseased arterial segments. The authors applied the Agatston definition and categorized studies into those with a high- and low-calcium grade for EVT application. No significant intergroup differences were observed in amputation-free survival and life expectancy at 1 year, in contrast to patency of the treated segments and wound healing, which showed statistically significant differences.[23]

All these analyses certainly gather indisputable advantages and inherent drawbacks in interpretation. However, an integrated, standardized, and widely accepted calcium scoring system and indexation is currently unavailable for the entire, or specific, zones of the inferior limb. Unfortunately, a high-specificity calcium score in a quantitative, regionally applied strategy and evaluation (BTK vs BTA, distinctly) is currently unavailable.

Clinical implementation of each individual calcium index (CaI) may be useful to clinicians and interventionists in the future. Following already described cardiological indexing models, the specific association of the CaI with parallel BTA arterial stiffness evaluation (the pulsatility index [PI]), in addition to concomitant distal "run-off" and "collateral resistance" evaluation, can be predicted and analyzed in future studies.[22-25] This combined morphological and physiological calcium-dependent evaluation may eventually change current indications, feasibility rates, and prognosis in EVT interventions for CLTI.[5,16,23]

The current understanding of MAC as an independent etiopathogenetic contributor to arterial obstruction has gradually sidelined the previous concept of the dominant role of Type I atherosclerotic intimal arterial calcification (IAC), which is historically described in patients with peripheral arterial disease (PAD).[18] However, it should be emphasized that the lack of standardized and unanimously validated BTK and BTA calcification scores currently restricts the applicability of several endovascular devices that are under clinical evaluation for the management of CLTI.[17]

Pathophysiological features. As with all important biological models, a dual concomitant interpretation of both structural and functional pedal flow characteristics may enable better understanding of the patient's condition, indications for treatment, and prognosis. For any individual angiographic pattern of foot perfusion, it appears important to perform parallel hemodynamic evaluation for accurate diagnosis.[4] In patients with CLTI, the BTA functional flow should be evaluated in close association with the individual's systemic cardiac output, the patient's metabolic status, and with all wound-associated pathologies, such as microangiopathy (medial arterial sclerosis), diabetic peripheral neuropathy,[20,21] tissue necrosis, inflammatory edema, and local sepsis.[21,24]

In the CLTI foot, the skin, muscles, and nerves become terminal, or end-organ territories with poor flow-compensatory capacities.[5,6,24] Maintaining vital levels of perfusion depends on individual collateral reserve (lasting functional collaterals) and available arteriogenesis and angiogenesis capacities.[24-27] This is particularly apparent in patients with diabetes who present with collateral depletion associated with MAC, local septic thrombosis of small collaterals in the vicinity of wounds, and abolished collateral regeneration that characterize the metabolic syndrome.[24,25] In diabetic limbs owing precarious collateral support "a few millimeters of the skin, up to the entire foot may depend on one specific end-territory vessel" according to the EAOD concept described by O'Neal et al.[25]

The foot arches connect the pedal trunks, store and circulate pulsatile blood and kinetic flow energy throughout the foot tissues (similar to the circle of Willis in the brain), and play the functional role of a collateral hub of the foot. However, CLTI injures the foot arches and interferes with efficient functioning of these important structures.[16,24,25]

The current non-invasive macro-microvascular functional evaluation of perfusion of the calf and foot[26] represents a standardized and mandatory diagnostic tool in patients with CLTI. However, the following are several limitations of this current assessment: (1) owing to local diabetic or renal calcifications and arterial non-compressibility, the ankle-brachial index (ABI) is less useful in these patients and probably better replaced by the toe-brachial index (TBI); (2) heavy calcification and random survival of foot collaterals also restrict ankle pressure (AP) and toe pressure (TP), which interferes with assessment of regional foot perfusion;[26] (3) transcutaneous oximetry ($TcPO_2$) is strongly dependent on local temperature, foot edema, inflammation, and vasoconstriction;[26] and (4) laser Doppler flowmetry, near-infrared spectroscopy (NIRS), and tissue oxygen saturation (StO_2), or implantable oxygen microsensors (O_2MS) provide accurate topographic flow assessment but are beneficial only for analysis of relatively shallow tissues; these microvascular exams are also affected by the wound extent, depth of necrosis, and local edema and inflammation.[4,26]

Significance of terminal-type foot flow in current clinical practice. The pedal flow manifests a typical end-territory peculiarity by native and acquired hampered capacity of collateral compensation in CLTI.[5,6,24,26] In normal conditions, BTA systolic pressures steadily decrease (100 mm Hg in the pedal trunks corresponding to 80 mm Hg in the foot arches, 60 mm Hg in the collaterals, and 30 mm Hg in the capillaries).[24,27] Pedal flow is completely dependent on the upstream tibial vessel diameter and rigidity (particularly in diabetic and renal patients),[23,28] on the individual's cardiac output,[27] and on specific foot territorial vascular resistance.[26-28] For example, a 50% loss of foot collaterals

may be associated with a 5- to 10-fold increase in the distal foot run-off resistance, despite successful EVT recanalization or bypass revascularization.[24,29,30]

Achievement of a physiological pulsatile flow to the CLTI-threatened foot remains a challenging aspect of BTA revascularization. Venous bypass is considered the anatomical and physiological gold standard for distal foot reperfusion;[4] however, this approach depends upon the available foot run-off,[4,7,13] the patient's general condition (the Patient risk, Limb severity, and ANatomic complexity [PLAN] GVG recommendations),[4] and availability of a correct venous conduit.[4]

EVT offers a comparable alternative, albeit with a lower pulsatility flow, that is dependent on local vessel stiffness and calcification burden; resulting angioplasty flow enhances lower local arteriogenesis (reduced arterial wall shear stress), and unchanged distal collateral resistance and perfusion pressures.[1,23,27,28] High pedal arterial wall rigidity, with significantly stiff run-off collaterals, may lead to laminar flow perfusion in the newly recanalized foot arteries and early vessel thrombosis.[30-33]

Pedal arteries show high inherent perfusion resistance (resistance of the dorsalis pedis is 2-times higher than that of the abdominal aorta), and also acquired high perfusion resistance as a result of progressive medial sclerotic changes (approximately 3-times higher stiffness than that of the corresponding in-flow femoral artery in the same individual).[28,32,33] These changes indicate a loss of kinetic energy, loss of pulsatile flow, and reduced collateral perfusion.[32,33] For example, 80% pedal stenosis may cause 10-times greater kinetic energy loss than similar 80% femoral narrowing secondary to higher stiffness and lower pulsatility flow.[33]

Vessel pulsatility appears to be a significant hemodynamic marker with equal importance in pedal arterial circulation, particularly following pedal artery percutaneous transluminal angioplasty (PTA).[28]

A standardized pulsatility index (PI) could be estimated using the Duplex peak systolic velocity (PSV) and pondered to negative diastolic velocity (NDV).[31,32] PI may be a reliable minimally invasive functional indicator with good reproducibility among patients with CLTI.[31,32] Individual PI can accurately predict major adverse cardiac and vascular events[31,32] and can provide a linear dependence to local foot arterial resistances; it adds complementary information in addition to the CI, before and after BTA angioplasty application.[28,32,33]

The peripheral fractional flow reserve (PFFR) using trans-stenotic distal/proximal pressure measurements[34-36] and territorial oxygen uptake calculation (using magnetic resonance imaging [MRI]) are 2 innovative flow-diagnostic methods that are useful for accurate collateral reserve evaluation.[5,34] These measurements reveal that tissue oxygen distribution is a time-dependent and multifactorial process varying before, during, and following revascularization,[5] often without linear correlation with apparently "appropriate" macrovascular angiographic results. Several recent studies[34-36] have reported the usefulness of infragenicular PFFR determination for peripheral functional flow evaluation.[34-36] However, current clinical application of PFFR remains limited with regard to the tibial trunks (Level II) and still unavailable for the pedal arteries, the foot arches, and the large collaterals (Level III of arterial division). A recent study performed by Ruzsa et al. included PFFR evaluation in infragenicular arteries in 39 patients.[36] The authors observed no differences between PFFR and other currently used physiological diagnostic methods (laser Doppler and $TcPO_2$) during the preoperative period, although with significant postangioplasty changes, with higher accuracy in the PFFR group.[36]

These findings can be illustrated through comparison between 2 patients showing similar Type 2A anatomical arch patterns (Kawarada classification)[11] and 2 others with a Type 2B pattern, with 2 others showing Type 3 arch morphology (**Figure 3**). Although each pair of patients (2 patients for each Type 2A, 2B, and 3) show equivalent anatomical lesions (perfectly matched with each Kawarada type of angiographic features),[11] each pair may express persistent foot-flow differences from a

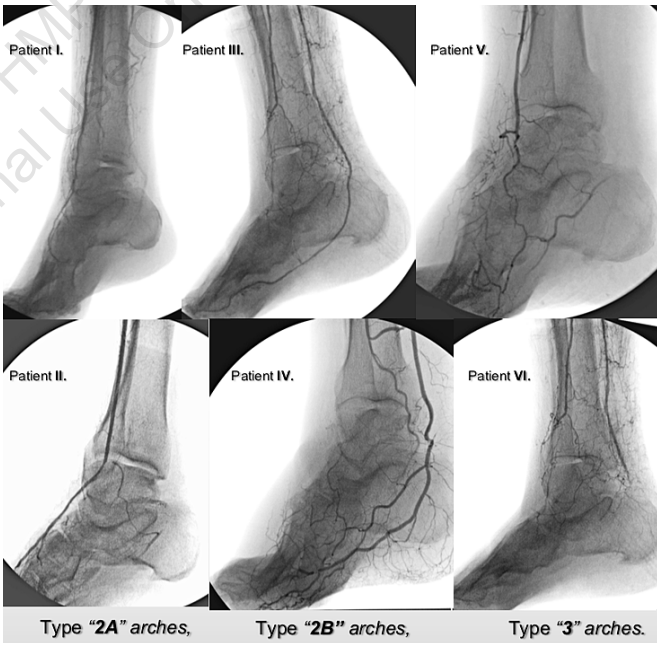

FIGURE 3. An example of analogous foot arch anatomical features that may hold distinct parallel functional (hemodynamic) characteristics. A comparison is made between 2 patients having analogous Kawarada "Type 2A" arch patterns (Patients I and II), with 2 others showing parallel "Type 2B" lesions (Patients III and IV), and with 2 others displaying similar "Type 3" arch morphologies (Patients V and VI). Although their arch anatomical findings appear similar in each pair of patients, their functional (hemodynamic) flow features may have questionable dissimilarities, by different foot calcifications loads, disparate pedal artery stiffness and peripheral resistances, and by individually different status of collateral loss. Although each pair is united by similar morphological characteristics, they may still remain different CLTI patterns from a physiological perspective.

physiological perspective, by disparities in wall stiffness and pulsatility indexes of foot arches, by different CI, PI, and PR, and by disparate resulting LBP and time-to-healing expectancies. In this example, all of these functional indicators provide accurate information regarding the hemodynamic perspective for each pair of selected patients, which is actually missing in current angiographic CLTI evaluation.

Future research in CLTI should focus on associating physiological indicators to parallel anatomical grading systems in unitary scales, with unitary conceptualization of CLTI indispensable for improving clinical outcomes.

Chronic limb-threatening ischemia assessment: insights and perspectives. Much progress has been made in this field to offer a better understanding and grading of the anatomical aspects of CLTI in the BTK[4] and BTA[4,8,11,15] main arteries; however, an accurate anatomical stratification (in a multilevel arterial occlusive disease perspective) combined with parallel functional evaluation is still awaited in current clinical practice.[2,4,37]

As shown in **Figure 4**, accurate information regarding the real involvement of the CLTI foot should probably associate detailed angiographic arterial branching evaluation, complementary calcific burden indexation, and individual functional PFFR characteristics in a whole understanding and apprehension of ischemic features for treatment.

This novel, multifaceted perspective may finally change in future studies some of the current traditional CLTI principles of standard evaluation and care.

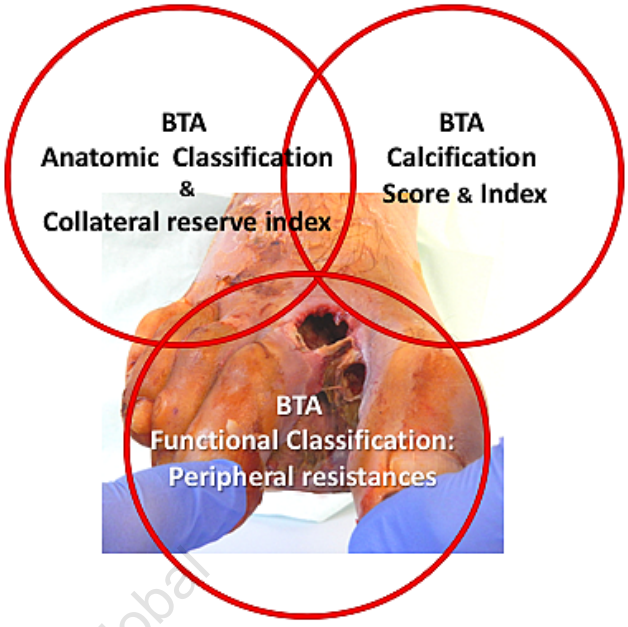

Figure 4. A chart model for prospective pedal artery flow appraisal. A complete foot-flow assessment in CLTI should probably include a multifaceted analysis assembling a detailed angiographic arterial branch stratification, a complementary calcific burden indexation, and individual functional flow evaluation, including the "collateral reserve" and PFFR characteristics, all perceived in a compounded understanding and indication for treatment.

Conclusion

BTA chronic arterial occlusive disease includes complex anatomical and functional pathological features and shows varied clinical presentations. Thorough morphological and hemodynamic evaluation of all CLTI effects is important and should include multilevel arterial branching disease classification, standardized calcification indexation, and commonly accepted functional foot flow evaluation. Future studies are warranted to gain deeper understanding of these preliminary concepts and the rationale for a wider diagnostic perspective in contemporary CLTI treatment.

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