Contemporary Infrapopliteal Intervention for Limb Salvage and Wound Healing
– Harmonization of Revascularization and Wound Management –

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Infrapopliteal arterial disease is a significant cause of critical limb ischemia (CLI), whether single-segment or multi-segment disease. The collaboration between the tremendous advancements in endovascular technology and the refinement of endovascular techniques has renewed the classic infrapopliteal interventions during the past decade. With this paradigm shift in the treatment of CLI, the role of a comprehensive approach of different disciplines for tissue loss is becoming greater. Given the increasing global burden of CLI, we review the cutting-edge diagnostic and endovascular approaches to infrapopliteal artery disease, and the importance of wound management in optimizing clinical outcomes. 

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Key Words: Critical limb ischemia; Endovascular therapy; Infrapopliteal artery disease; Tissue loss

There is an increasing global burden of peripheral artery disease linked with diabetes mellitus and chronic kidney disease.1-3 With these pandemic conditions, critical limb ischemia (CLI), the most advanced stage of peripheral artery disease, is an emerging public health issue. Recently, the prevalence and incidence of CLI were reported to be 0.23% and 0.20%, respectively, in those over the age of 65.4 It is an urgent requisite.

As infrapopliteal artery disease is the mainstay of CLI, whether in single or multiple segments,5-7 bypass surgery has been a traditional treatment option, especially for patients without severe comorbidities who can tolerate general anesthesia and an invasive procedure. However, the collaboration between advanced technology and technical refinement has led to sophisticated classic infrapopliteal interventions.8-18 More recently, even below-the-ankle interventions have been advocated for the treatment of symptomatic pedal artery disease.17-22 Updated guidelines have asserted an expanding role of endovascular therapy for the treatment of CLI in patients on the verge of major amputation and at high risk for cardiovascular events and death.23-24 According to the ACC/AHA guideline, the endovascular option is primarily recommended for patients with an estimated limited life expectancy within 2 years. Furthermore, according to the ESC guideline, emphasis is placed on an “endovascular-first” strategy if technically feasible. In cases of failed bypass, endovascular back-up also could be a last resort. With this paradigm shift in the treatment of CLI, the significance of wound issues has increased. This review describes the cutting-edge diagnostic and endovascular therapeutic approaches to infrapopliteal artery disease, and the extensive role of proactive wound management in order to optimize clinical outcomes.

Appreciation of Anatomy and Variants on Based on Angiography

Despite the expanded armamentarium of less invasive diagnostic techniques, catheter-based infrapopliteal angiography using digital subtraction angiography technology remains the gold standard for accurate diagnosis and planning of endovascular procedures, which are mostly ad hoc interventions. As complex lesions in association with myriad collateral circulation are predominant in infrapopliteal artery disease, appreciation of the anatomy based on angiography is requisite for improving interventional outcomes. In patients with renal failure, carbon dioxide infrapopliteal angiography might be considered in order to prevent contrast nephropathy.25

Infrapopliteal angiography requires an optimal projection for each segment. The contralateral anterior oblique view is indispensable for appreciation of the positional relationship...
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Figure 1. Standard infrapopliteal anatomy in the left leg on digital subtraction angiography (anteroposterior view). (A) Proximal, (B) distal. (C) Typical angiographic appearance in infrapopliteal artery disease. Note the distal segments of anterior tibial artery (→) and posterior tibial artery (▲) are supplied through the collateral vessels from the peroneal artery (➡). (D) Development of collateral circulation in pedal artery disease. In this case, the medial tarsal artery develops to the lateral planter artery and the deep plantar arch as a collateral source because of the diseased dorsalis pedis artery. (E) Representative case of underlying infrapopliteal variant (cited from reference 26). Diagnostic angiography of the right leg shows multiple severe stenoses in the proximal peroneal artery and the paramalleolar posterior tibial artery (→). Note that chronic total occlusion with poor collateral vessels (➡) in the distal peroneal artery angiographically appears to connect with the dorsalis pedis artery (▲). The anterior tibial artery is considered to be hypoplastic. (F) Lateral plantar artery supplying blood flow to the toes in the case of occlusion of the dorsalis pedis artery. Although the dorsalis pedis artery is occluded, the prominent lateral plantar artery (large arrow) is the main supply to the toes through the metatarsal arteries originating from the deep planar arch (small arrow). (G) The dorsalis pedis artery supplying blood to the toes in the case of occlusion of the lateral plantar artery. Note that the dorsalis pedis artery (large arrow) alternatively supplies blood flow to the toes through the metatarsal arteries from the deep plantar arch (small arrow).
between the distal popliteal artery, the proximal anterior tibial artery and the tibioperoneal trunk, whereas the ipsilateral anterior oblique view is ideal for differentiation of the tibioperoneal trunk, the proximal posterior tibial artery and the peroneal artery. Also, contralateral anterior oblique and ipsilateral cranial views can provide a better understanding of the distal crural artery and the pedal arch conditions. Standard anatomy is shown in Figures 1A, B. In cases of occlusive lesions in both or either of the anterior tibial artery or posterior tibial artery, which is a typical pattern of severe infrapopliteal artery disease, the peroneal artery can serve as a collateral source (Figure 1C). In cases of pedal artery disease, the foot artery branches such as the medial and lateral malleolar arteries, the medial and lateral tarsal arteries, and the arcuate artery can be developed as collateral sources (Figure 1D). The foot artery branches and digital arteries might not be angiographically visible because of occlusive lesions, occult vessels or their absence.

Variants in the popliteal artery branching pattern consisting of aplasty or hypoplasty of the tibial artery, high take-off of the tibioperoneal arteries, trifurcation and an anterior tibioperoneal trunk are not uncommon.26 Given that approximately 10% of the population has these variants, differentiation of occlusion and variation represents a challenging task in cases of severe infrapopliteal artery disease. When an infrapopliteal variant is observed in 1 extremity, there is a 28–50% probability of the same pattern on the other side. With the features of infrapopliteal variant vessels in mind, insight into the possibility of underlying variations is the key to successful identification of infrapopliteal variants (Figure 1E).

Furthermore, the greater variation in the foot arteries, especially on the dorsum, can be confusing because the standard pattern of distribution of the branches of the dorsalis pedis artery is not common.27 Each toe can be supplied via metatarsal arteries from the dorsal or plantar system depending on the dominance of supply and the extent of occlusive lesions (Figures 1F, G). Similarly, the hallux can be supplied by the medial plantar artery, the plantar metatarsal artery from the lateral plantar artery and the dorsal metatarsal artery from the dorsalis pedis artery, depending on the dominance of supply and the extent of occlusive lesions.

**Indications and Goals of Revascularization**

Clinically, rest pain and tissue loss (ulcers and gangrene) are definite indications for infrapopliteal intervention. In patients with multisegment disease, the general rule is to increase upstream flow to the greatest extent possible by first treating significant suprapopliteal lesions. The time interval between suprapopliteal and infrapopliteal interventions can vary according to clinical manifestations, the status of ischemia, and the op-
In infrapopliteal intervention and wound management, infrapopliteal intervention can also serve as a bridge therapy to bypass surgery after the achievement of infection control. In cases of the need for frequent repeat intervention during a short time, shifting treatment toward the surgical option can be considered if the patients can tolerate general anesthesia and bypass surgery with good risk.

In our practice, dual antiplatelet therapy is given at least 2 days before the procedure and continued until 30 days after the procedure. Also, a relatively low-dose (3,500–5,000 IU) of heparin appears to be acceptable for Japanese patients undergoing current lower limb interventions. However, there is no consensus regarding the established protocol of antiplatelet therapy and heparinization.

Stenotic lesions can be crossed in the same fashion as in a coronary intervention. With the advent of dedicated guidewires, a variety of crossing techniques have emerged in the field of infrapopliteal intervention (Figure 3). Antegrade approach using a variety of techniques (stand alone or combination) can be primarily considered. Just in cases of failed antegrade crossing, a retrograde approach can be considered. CART, controlled antegrade and retrograd tracking and dissection.

Endovascular Crossing Technique and Management of Complications

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Stenotic lesions can be crossed in the same fashion as in a coronary intervention. With the advent of dedicated guidewires, a variety of crossing techniques have emerged in the field of infrapopliteal intervention (Figure 3). In the clinical setting, combining these techniques may increase the success rate of crossing, and intraluminal or subintimal tracking can occur in either direction and with each type of technique. Thus, different scenarios can be observed during the passing of CTO lesions (true-to-true, true-to-false-to-true, etc). In a challenging calcified CTO, a loop technique potentially carries the risk of breakage of the guidewire or inability to remove the curled tip of guidewire. Besides vascular access complications and contrast-induced nephropathy, knowledge of the complications of infrapopliteal intervention is indispensable for interventional cardiologists.

Vessel spasm can occur in less calcified vessels and may compromise flow when delivering equipment or performing intervention. In infrapopliteal intervention can also serve as a bridge therapy to bypass surgery after the achievement of infection control. In cases of the need for frequent repeat intervention during a short time, shifting treatment toward the surgical option can be considered if the patients can tolerate general anesthesia and bypass surgery with good risk.
Emerging Endovascular Technology

Balloon angioplasty is notorious for its high rates of restenosis (50–70%) and reintervention (approximately 50%) within 6–12 months, but it can achieve acceptable limb salvage rates.\(^{35,37}\) (Figure 4). Bare metal stents (BMS), whether balloon-expandable or self-expandable, have also failed to significantly improve restenosis rates (=50%), although the use of a scaffolding device for an acute result is attractive (Figure 4).\(^{38,39}\) Thus, liberal use of reintervention has made infrapopliteal intervention a viable option.

Currently, there are 3 major approaches to maintaining infrapopliteal vessel patency. First is the use of a drug-eluting balloon (DEB) designed to release paclitaxel into the media of the angioplasty site to reduce the restenosis from neointimal hyperplasia by suppressing smooth muscle proliferation. A wide range of DEBs is available to accommodate the unique anatomy of the calf and foot in terms of vessel size and length. The benefits of DEBs are definitely attractive: comparably low cost, avoidance of local inflammation caused by drugs or polymers for months or years, freedom from permanent stent fracture events, no residual metal struts, and accessibility for reintervention compared with stent implantation. Recent studies with mean lesion lengths >100 mm reported restenosis rates <30% compared with 70% for balloon angioplasty (Figure 4).\(^{39,41}\) In the DEBATE BTK trial (a randomized, open label, single-center study comparing DEB and balloon angioplasty), binary restenosis, assessed by angiography in >90% of patients, occurred in 20/74 (27%) lesions in the DEB group vs. 55/74 (74%) lesions in the balloon angioplasty group (P=0.001).\(^{41}\) From the procedural standpoint, there are still some flaws that might cause subsequent acute or late lumen loss by vessel dissection, vessel elastic recoil, or aneurysmal formation. Furthermore, several randomized controlled trials of DEBs vs. standard balloons are currently ongoing to demonstrate the considerable potential of DEBs. Also, the potential risk of vasculitis because of distal embolization of the active drug and excipient coating is a major concern with this new technology.\(^{42}\)

Second, the drug-eluting stent (DES) technology that has revolutionized coronary intervention has been adopted to treat infrapopliteal lesions. As in the coronary setting, the superiority of DES over BMS or standard angioplasty has been proven for infrapopliteal lesions. Recent randomized controlled trials with mean lesion length <50 mm reported approximately 20% restenosis rate for DES at 12 months while BMS showed approximately 50% (Figure 4).\(^{43-45}\) Furthermore, the YUKON BTK study reported a clinical benefit of DES that was a significantly lower amputation rate compared with BMS (5.3% vs. 22.6%, P=0.04).\(^{46}\) However, most DES currently used in the lower leg were designed for the coronary arteries. Infrapopliteal arteries, especially the distal segments, are susceptible to multiple types of mechanical stress such as flexion, torsion, expansion and contraction because of ankle joint movement and compression by surrounding inflexible tendons, tough ligaments and solid bones. This unique situation can increase the potential risk of stent deformities such as stent compression and stent fracture, especially in the distal calf and foot.\(^{12,47}\) Thus, the development of DES platforms designed specifically for the infrapopliteal arteries are necessary.

Thirdly, the bioresorbable vascular scaffold (BVS) is an emerging technology to overcome stent-related issues. ABSORB BTK is a prospective, single-arm, multicenter trial designed to evaluate the safety and efficacy of the Absorb\(^\text{TM}\) BVS.\(^{48}\) The device has been implanted in up to 90 CLI patients with symptomatic infrapopliteal artery disease in up to 10 clinical trial sites. The primary endpoint is a composite of freedom from...
Application of Practical Endpoints and Clinical Outcomes

Measurement of the microcirculation is a reasonable, objective endpoint to assess the effects of revascularization. Clinically, MALE, consisting of reintervention and major amputation, is a proposed objective endpoint in CLI studies. However, in the clinical setting, reintervention is quite straightforward, and the clinical significance of the need for reintervention is different from that of major amputation for CLI patients.

On the other hand, single endpoints such as the amputation-free survival rate, limb salvage rate, and freedom from major adverse limb events (MALE; major amputation or major reinterventions) within 1 year, or death within 30 days of the procedure. This technology might present a novel option in the treatment of infrapopliteal artery disease.

These promising data regarding restenosis rates and vessel patency allow us to expect a significant reduction in clinically-driven reintervention. Thus, the clinical performance of emerging endovascular technology needs to be addressed in terms of wound healing, limb salvage and the cost-benefit trade-off for the use of the technology.
points. Moreover, the freedom from reintervention rate was 55.0%, 49.6%, 44.4%, and 36.1% (Figure 5A). These findings suggest a substantial discrepancy between freedom from reintervention and avoidance of limb loss, and that the sustained limb salvage rate is related to poor survival and the effects of the competing mortality hazard.

In the clinical setting, “complete wound healing” after intervention rate can offer a better understanding of the clinical landscape after successful infrapopliteal intervention. In a recently published practical study in which stenting was required in 43% of patients during the entire clinical course, amputation-free survival rates were 85.7%, 68.0%, 54.5%, and 39.8% at 6 months, 1, 2, and 5 years, respectively, while limb salvage rates were 96.0%, 92.4%, 86.3%, and 86.3% at the same time points. Moreover, the freedom from reintervention rate was 55.0%, 49.6%, 44.4%, and 36.1% (Figure 5A). These findings suggest a substantial discrepancy between freedom from reintervention and avoidance of limb loss, and that the sustained limb salvage rate is related to poor survival and the effects of the competing mortality hazard.

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Occclusive disease. Vessel calcification, endothelial dysfunction, subsequent thrombosis formation, and vasoconstriction can disturb both the macrocirculation and microcirculation. Foot ischemia can be further impaired by neuropathy; arterio-venous shunting because of autonomic neuropathy, exogenous factors such as excessive loading because of motor and sensory neuropathy and diabetic foot deformity can cause neuroischemic ulcer or gangrene. Also, hyperglycemia and impaired immunological responses can dispose purely ischemic wounds to becoming infected ischemic wounds, and subsequent infectious arteritis in the small arteries of the foot can exacerbate ischemia. Consequently, polymicrobial foot infections can range from minimal superficial infection to deep infection including osteomyelitis, and serve as a physical bar-

dovascular therapy can also be an important endpoint for CLI patients with tissue loss because incomplete wound healing is not necessarily an indication for major amputation. It is worthwhile to note that the wound healing rate ranges between 50% and 90% wherever limb salvage rate is approximately 80–90% (Figure 5B). As for wound healing time, the mean time to complete wound healing is 4.8 months, with healing rates of 14.2%, 36.8%, 57.5%, 67.9%, and 73.6% at 1, 3, 6, 9, and 12 months, respectively. In particular, diabetic foot and infectious wound as well as pedal arch disease are independently associated with clinical outcomes even after a successful infrapopliteal intervention (Figures 5C, D).

In Japan, there is almost unlimited availability of medical care for hemodialysis (HD) patients. However, few data are available regarding the outcomes of infrapopliteal intervention for CLI patients on HD. Technical success rates might be lower for HD than for non-HD patients, and HD patients may have several times the risk of wound non-healing, the need for re-intervention, and death or major amputation (amputation-free survival) than patients who do not have endstage renal disease.

Multidisciplinary Approach for Ischemic Wound With Diabetes Mellitus and Infection

A qualified specialty that organizes multidisciplinary care for wounds should be established in each vascular center. Even though tissue loss is complicated by diabetes mellitus and infection, an individualized approach with specialized physicians (plastic surgeon, dermatologist or orthopedic surgeon etc) and nurses can enhance the possibility of clinical success (Figures 6A, B).

Diabetes mellitus can change the nature of infrapopliteal
rier to re-epithelialization and amplify the risk of sepsis. However, liberal removal of the devitalized tissue, empirical or sensitivity-based antibiotic treatment, and epithelialization-stimulating dressings have been proven to improve wound healing and limb salvage rates. In cases of severe infection, the priority of treatment is temporary debridement/minor amputation before revascularization in order to prevent the development of sepsis. In cases of uncontrollable infectious tissue loss, major amputation or terminal care can be considered for patients who are not eligible for any revascularization.

**Controversy Over the Angiosome Theory**

The original concept of the angiosome, introduced by Taylor and Palmer in 1987 in the context of flaps for skin healing, is a “3-dimensional (3D)” composite of skin, soft tissue, and bone supplied by a single source artery and its branches. Although even the original concept of a 3D angiosome might be less relevant to the in vivo blood supply than to flap design, the recent concept of a “2-dimensional (2D)” angiosome as a uniform map of vascular territories with clear boundaries emerged in the field of surgical and endovascular treatment for CLI 5 years ago. Despite the lack of randomized comparative studies, emphasis was placed on direct revascularization of the artery feeding the 2D angiosome where ischemic ulcers or gangrene exists rather than indirect revascularization. In the middle of the current angiosome boom, more recent studies have raised objections to this approach that sound good in theory. These differences in the benefits of the 2D angiosome theory in published studies could be related to the multifactorial nature of CLI. Of great interest, the most recent study using SPP found no significant difference in microcirculation between direct and indirect revascularization, and that approximately half of the feet revascularized had a change in microcirculation that was not consistent with the 2D angiosome theory. As such, the original complex ischemic limb has an individual 3D angiosome makeup (Figure 7), even the 3D angiosome theory might be an adjunctive concept to providing an excuse for insufficient hemodynamic outcome following angiographic success and provide a hint as to further endovascular strategy.

**Conclusions**

Amid a pandemic of peripheral artery disease, contemporary catheter-based intervention is a paradigm shift in the treatment of symptomatic infrapopliteal artery disease. From a clinical perspective, the increasing popularity of infrapopliteal intervention heightens the importance of proactive wound management as stand-alone endovascular procedure does not necessarily facilitate clinical success following procedural success (Figure 8). Therefore, harmonization of revascularization and wound management in a coordinated approach is indispensable in the treatment of CLI.

**References**

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