REVIEW PAPER

The role of percutaneous balloon angioplasty in the treatment of critical limb ischemia in diabetic patients

Michał Olszewski[1], Grzegorz Dziwiszek[1], Dariusz Świtaj[1], Zbigniew Brzostek[1], Joanna Olszewska[2], Leszek Czupryniak[3], Ireneusz Nawrot[4]

[1]Department of General and Vascular Surgery, Mazovia Hospital, Ostrołęka, Poland
[2]Department of Cardiology, Mazovia Hospital, Ostrołęka, Poland
[3]Department of Diabetology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland
[4]Department of General, Vascular, and Transplant Surgery, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Critical limb ischemia (CLI) is the most advanced form of occlusive peripheral artery disease and often leads to amputation. The prognosis is significantly worsened in patients with diabetes as without intensive management > 50% of patients die within one year of CLI onset or have to undergo a lower extremity amputation. In diabetes CLI is mostly present as diffuse, long-segmented occlusions in two or three arteries of the lower leg, which may co-exist with significant atherosclerosis of the femoropopliteal segment and/or, less frequently, the iliac segment. Also, in diabetes CLI due to atherosclerosis limited to the tibial segment is significantly more common than in non diabetes individuals as well increased arterial wall calcification. These conditions affect the outcome of all revascularization techniques, including percutaneous balloon angioplasty (PTA). The effectiveness of balloon angioplasty as the essential technique for revascularization of below-the-knee arteries in diabetic patients has been confirmed as it repeatedly showed reduction of amputation rates. The latest developments include drug-eluting balloons which appear to be promising in terms of limiting the amount of restenosis. The article presents the current data on the efficacy and safety of PTA in patients with CLI.

KEY WORDS: diabetes, peripheral artery disease, percutaneous ballon angioplasty, critical limb ischemia.

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Introduction

Critical limb ischaemia (CLI) is the most advanced form of occlusive peripheral artery disease reflecting impaired limb perfusion, which prevents normal tissue metabolism. It is manifested as at-rest and nocturnal pain of more than 2 weeks duration and/or tissue loss (ulceration or gangrene), usually in the foot. Diabetes is associated with an approximately 4-fold higher risk of developing CLI [1], and next to tobacco smoking is the strongest risk factor. This is due mainly to micro- and macroangiopathy, which lead to tissue ischaemia, while co-existing neuropathy and immunosuppression additionally predispose to the development of diabetic ulcers that become infected. Also, patients with diabetes often have other risk factors for cardiovascular disease such as smoking, dyslipidaemia, or hypertension.

In terms of mortality and amputation rates, the prognosis for patients with diabetes and CLI is grave, often worse than the prognosis for patients with very aggressive malignant tumours. Without intensive management, over 50% of patients die within one year of CLI onset or have to undergo a lower-extremity amputation [1]. In patients with diabetic foot ulcers healed with appropriate therapy, 40%, 60%, and 65% of patients have a recurrence within 1 year, 3 years and 5 years, respectively [2], which explains the high amputation rates in this patient population. It is estimated that the total risk of amputation is approximately 15-fold higher compared with nondiabetic patients [3]. The independent predictors of amputation include diabetes duration, inadequate glycaemic control, microalbuminuria, retinopathy, neuropathy, absent pedal pulses, treatment with insulin, diabetic foot ulcers, and former amputation [4–6]. What is more, diabetic patients with ischemic ulcers have a significantly worse prognosis than those with neuropathic ulcers in terms of 5-year mortality (55% vs. 45%) and 5-year amputation rates (29% vs. 11%) [6].

With the characteristic course of atherosclerosis of the arteries of the lower extremities (peripheral artery disease) in diabetic patients, its surgical management is difficult and presents a challenge to vascular surgeons and interventional radiologists because it usually affects infrapopliteal arteries and is associated with significant vascular calcification.

In diabetic patients, CLI is mostly present as diffuse, long-segmented occlusions in 2 or 3 arteries of the lower leg, which may co-exist with significant atherosclerosis of the femoropopliteal segment and/or, less frequently, the iliac segment. In diabetic patients, however, CLI due to atherosclerosis limited to the tibial segment is significantly more common. Gray et al. observed that this patient population has a worse prognosis in terms of survival, survival with preservation of the limb, and risk for amputation, compared with patients with CLI caused by atherosclerosis involving, at the same time, both the tibial and the femoropopliteal segments. Although vascular involvement is then 'wider', the revascularization outcomes are better than in isolated tibial disease [7]. Graziani et al. found 2893 significant atherosclerotic lesions based on angiographic findings in 417 diabetic subjects with critical ischaemia corresponding to Rutherford 5 or 6. Of those, 74% were in infrapopliteal arteries and only 1% in the iliac arteries. The prevalence and length of arterial occlusions were significantly greater in distal vessels. Occlusions > 10 cm accounted for 50% of occlusions in infrapopliteal arteries and just 11% of occlusions in the femoral segment. Twenty-eight per cent of subjects had occlusions in all infrapopliteal arteries [8]. Mostly such occlusions are in proximal vessels, which become patent above the ankle joint as they are fed to some extent by collaterals. This often allows for survival of the limb free from tissue loss, but not for diabetic ulcer healing. Restoration of direct in-line blood flow to the arteries of the foot is therefore a crucial part of treatment for CLI in diabetic patients.

Increased calcification of the arterial wall is frequent in subjects with diabetes. This is related to a significantly greater prevalence of arteriosclerosis (medial arterial calcification, Mönckeberg's arteriosclerosis) which coexists with atherosclerosis obliterans. Arteriosclerosis is a condition affecting the middle layer of the arterial wall with its marked calcification and subsequent increased stiffness. Although arteriosclerosis does not significantly impair vascular patency, it is nevertheless a negative prognostic factor. Everhart et al. found that in diabetic patients with medial arterial calcification the mortality rate was 1.5-fold that of diabetic patients without medial arterial calcification and the rate of amputations was 5.5-fold that of diabetic patients without medial arterial calcification [9]. Calcification may affect any of the 3 layers of the arterial wall, and the calcium deposition as seen in both longitudinal and transverse sections is highly variable and irregular, which means that the resistance of the artery wall to the pressure generated by a balloon catheter also varies. As a result,

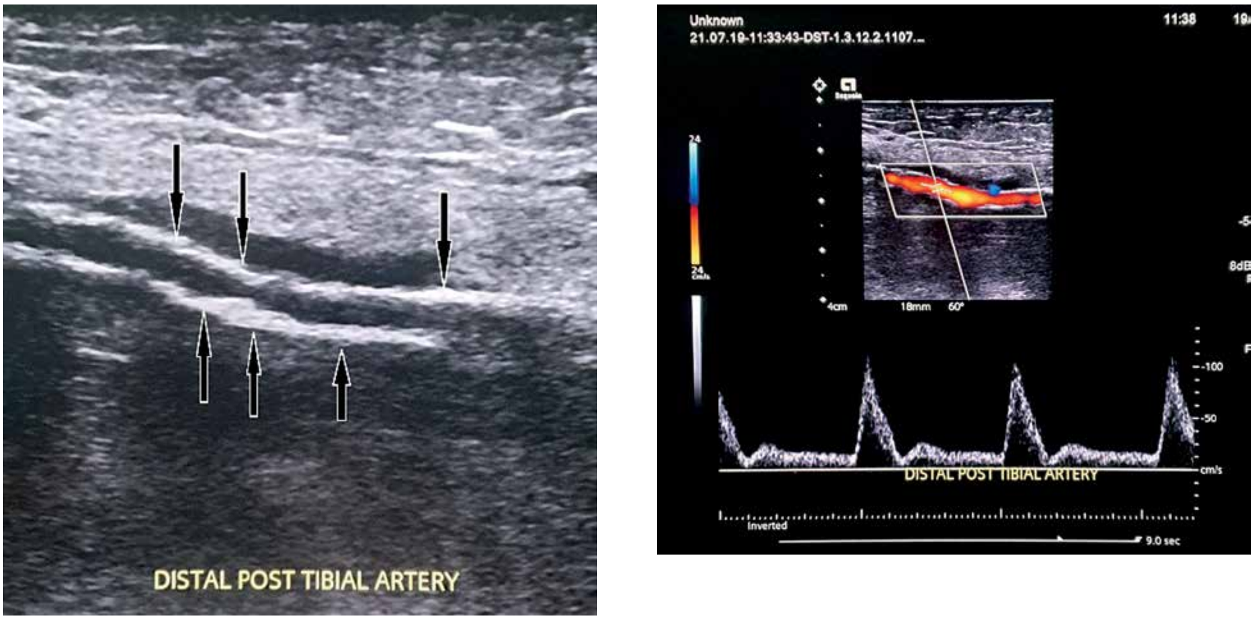

Figure 1. Calcification in the distal segment of the patent posterior tibial artery

the distribution of pressure vectors during balloon angioplasty is difficult to predict, which increases the risk for artery dissection, atherosclerotic plaque rupture, or distal embolization (Figure 1, 2).

Revascularization is essential in cases of CLI, especially when associated with diabetic ulcers. As confirmed by the studies cited above, very frequently it is necessary to restore adequate perfusion in the foot, which is impaired by long-segment, heavily calcified occlusions in more than one infrapopliteal artery. Not infrequently, foot ulcers are associated with gangrene and inflammation of adjacent soft tissue with edema, which may involve the lower limb above the foot. Because CLI is often seen in patients with additional cardiovascular risk factors or the elderly, 'open' revascularization and bypass surgery are risky, technically demanding, and in some cases not feasible. Endovascular revascularization of infrapopliteal arteries is now a treatment modality of choice. One obvious advantage is that most endovascular procedures can be performed with local anaesthesia. Additionally, postoperative recovery is significantly faster, which is especially important for patients who are older and have more comorbidities. The long-term out-

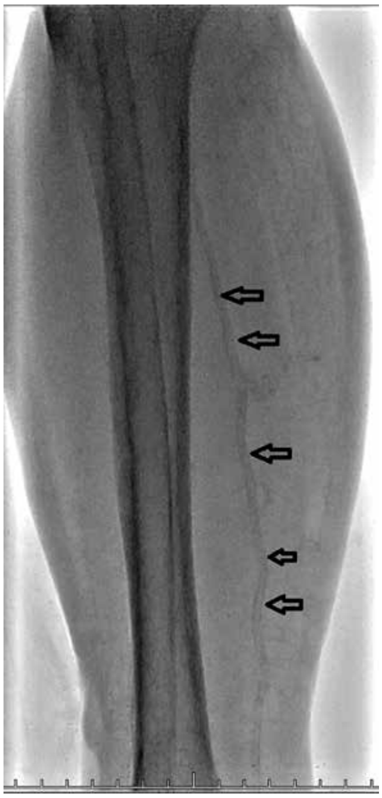

Figure 2. X-ray image showing calcification in the posterior tibial artery

Table 1. Indications for revascularization of infrapopliteal arteries

Indications for revascularization of infrapopliteal arteries	Aim
Critical ischemia Rutherford 4 and 5, and lesions in 1–3 infrapopliteal arteries	To provide in-line blood flow into the pedal arch
Critical ischaemia Rutherford 6, and lesions in 1–3 infrapopliteal arteries	To avoid a major amputation by improving blood supply to allow healing of minor amputation wound
Severe claudication Rutherford 3, and lesions in 2–3 infrapopliteal arteries	To improve the health-related quality of life by increasing functional claudication distance

comes of open surgery and endovascular treatment are comparable, but the latter is associated with a much lower risk of major perioperative complications, which translates into a larger proportion of revascularized limbs. Importantly, in cases of endovascular revascularization failure, bypass surgery is possible as re-intervention (Table 1).

The key indications for revascularization of infrapopliteal arteries include clinical assessment (non-healing or recurrent ulcers, or incomplete closure of an ulcer first healing as a result of former revascularization, rest pain) consistent with the results of accessory investigations (subcutaneous oxygen partial pressure [TcPO2] < 30 mm Hg, imaging findings of impaired vascular patency). When possible, an attempt should be made to improve foot perfusion to promote wound healing before a planned amputation of the forefoot to reduce the risk for a major amputation.

Key principles of revascularization

The key factors determining success of revascularization include the number of patent arteries on final postoperative arteriography and the specific artery (tibial vs. peroneal arteries), preserved blood flow in the pedal arch, status of small vessels in the foot responsible for adequate blood return, and how the blood flow to the foot is improved (direct, in-line blood flow or indirect, collateral blood flow).

The number of patent arteries following revascularization is very important for ulcer healing and limb salvage, which should be reflected in attempts to unblock as many arteries as possible. Complete revascularization, i.e. all 3 arteries patent, is superior to incomplete revascularization, while 2 patent arteries is better than just one patent artery, and one patent artery is better than no patent artery. Peregrin et al. found that percutaneous balloon angioplasty (PTA) resulted in limb salvage rates of 56%, 73%, 80%, and 83% in patients with none, one, two, and three patent infrapopliteal arteries, respectively [9]. Faglia et al. found that the risk of amputation increased eightfold for every occluded infrapopliteal artery. Importantly, restoring patency of the tibial arteries

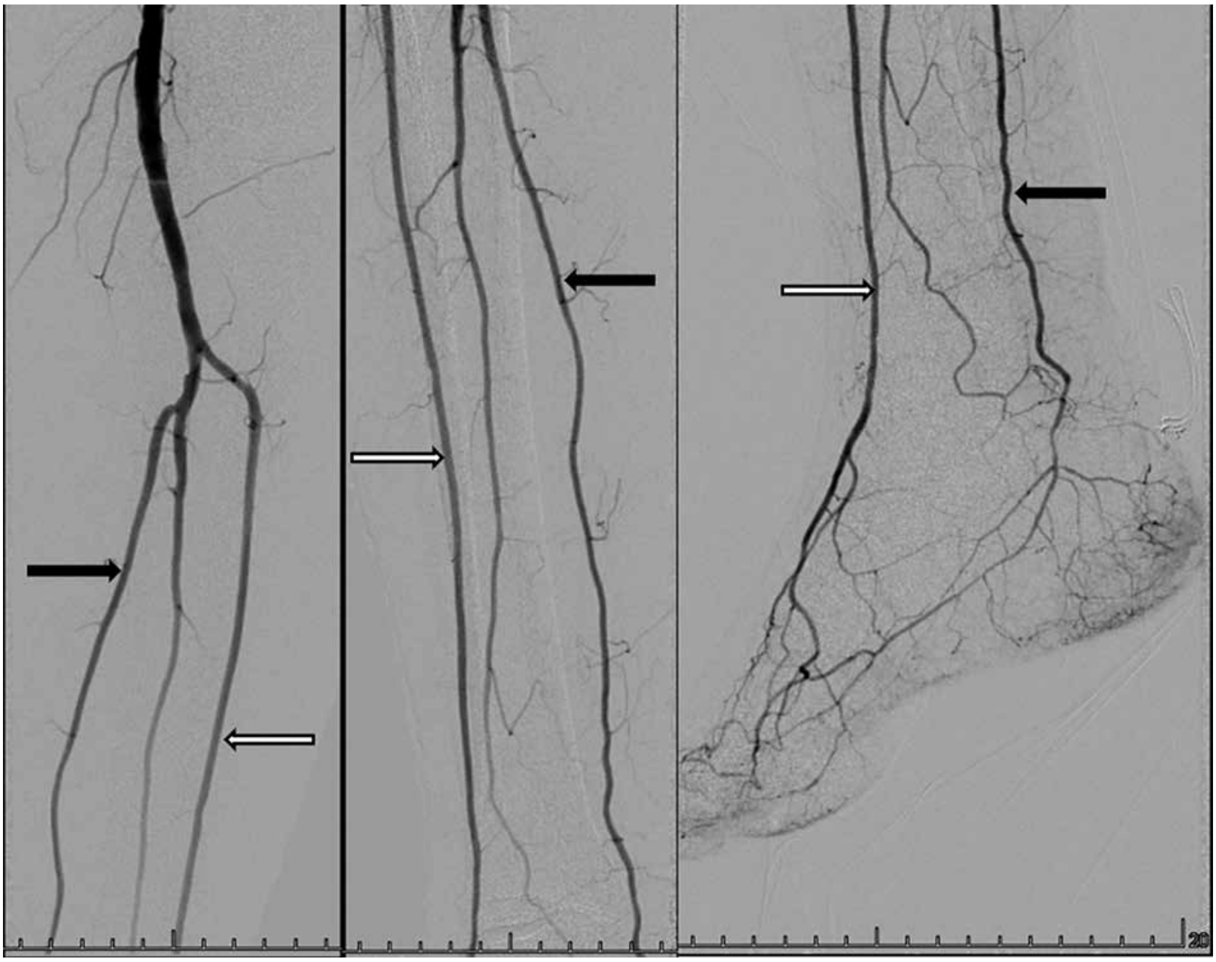

Figure 3. Normal angiogram showing the lower leg and foot with the complete pedal arch. The tibial arteries: anterior (white arrows) and posterior (black arrows)

Figure 4. Three-vessel revascularization. The left figure shows segments of the tibial arteries with multiple stenoses and segmental occlusions (black lines between arrows) and a high-grade, short-segment stenosis in the peroneal artery

Figure 5. Two-vessel revascularization. The left figure shows the occluded segment of the anterior tibial artery. No recanalization in the posterior tibial artery

(anterior and/or posterior) seems to be more effective than restoring blood flow in the peroneal artery alone. In their patients, PTA was effective in avoiding major amputation when recanalization occurred in at least one tibial artery, but not in all patients with recanalization of the peroneal artery alone [10] (Figure 3–6).

Recent studies underline the importance of direct in-line reperfusion of this part of the foot that is affected by ulceration. Taylor and Parker introduced the concept of vascular territories, or angiosomes, which are three-dimensional blocks of tissue (consisting of skin, subcutaneous tissue, fascia, muscle, and bone) fed by a source artery. According to this theory, each of the main below-the-knee arteries supplies a specific anatomic unit of the foot. There are six angiosomes of the foot and ankle, one angiosome originating from the anterior tibial artery, three angiosomes from the posterior tibial artery, and two angiosomes from the peroneal artery [11]. The entire dorsum of the foot is functionally one angiosome. The blood supply is provided by the dorsalis pedis artery, which is the continuation of the anterior tibial artery. The plantar foot encompasses 3 angiosomes fed by branch-

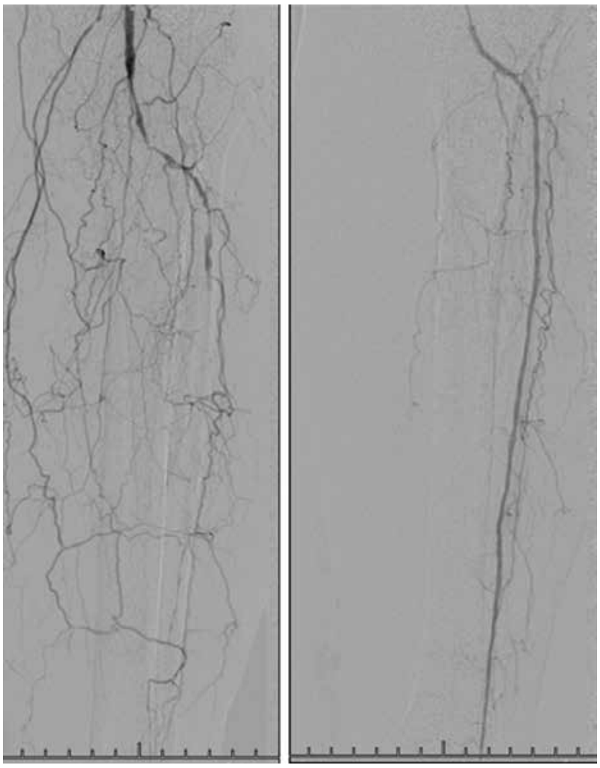

Figure 6. One-vessel revascularization. Recanalization of the anterior tibial artery. No recanalization in the posterior tibial and peroneal arteries, and the tibioperoneal trunk

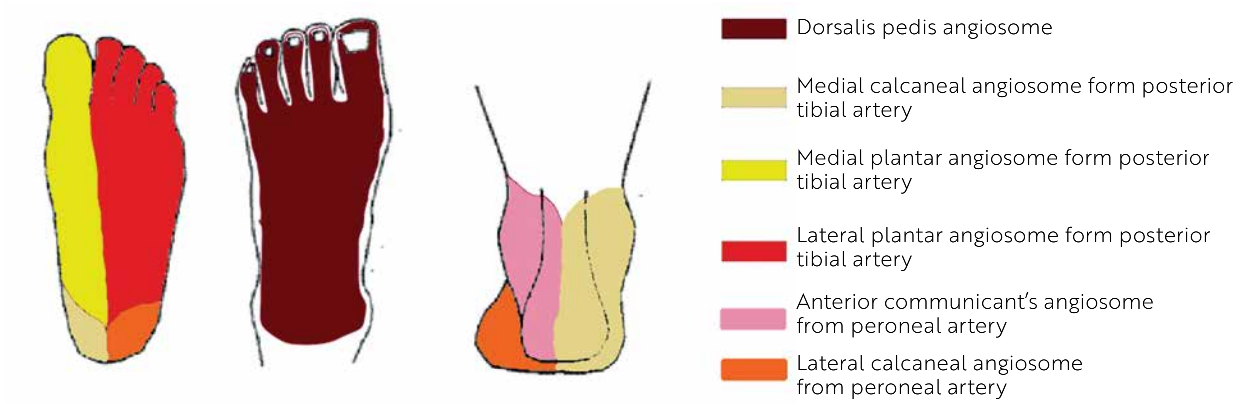

Figure 7. Angiosomes of the foot and ankle

es of the posterior tibial artery. The medial calcaneal artery supplies the medial ankle region and the medial heel. The medial plantar artery feeds the angiosome encompassing the medial sole of the foot, and the lateral plantar artery supplies the lateral aspect of the sole of the foot. The anterior, communicating branch of the peroneal artery supplies the lateral ankle, and the lateral calcaneal branch provides blood supply to the lateral aspect of the heel (Figure 7).

Neville et al. performed retrospective analysis of 52 nonhealing ischaemic wounds of the lower extremity in 48 patients who had had tibial bypass surgery. In the direct revascularization group (bypass to the artery feeding the affected angiosome) healing was observed in 91% of cases and with a 9% amputation rate vs. 62% healing and a 38% amputation rate in the indirect revascularization group (bypass unrelated to the affected angiosome) [12]. Better outcomes were also reported for endovascular procedures using an angiosome model of reperfusion and direct revascularization [13–16]. Iida et al. analysed 177 patients (Rutherford 5 or 6) who underwent endovascular treatment. Up to 4 years after the procedure, the limb salvage rate was 86% in the direct revascularization group vs. 69% in the indirect group, the difference being statistically significant [17]. Špillerová et al. in their retrospective analysis of 545 diabetic patients with CLI and tissue loss (Rutherford 5 or 6) also confirmed the superiority of direct angiosome-guided revascularization, especially in endovascular procedures [18] (Table 2).

Table 2. European Society for Vascular Surgery recommendation (2019)

Consider angiosome-guided revascularization in patients with significant wounds (e.g. WIfI wound grades 3 and 4), particularly those involving the midfoot or hindfoot, and when the target arterial path is available	Recommendation grade and level 2°C

However, angiosome-guided revascularization has some limitations, and a number of authors question its role as a key factor to obtain good outcomes [19]. The following arguments are voiced by the critics: tissue loss and or/gangrene sometimes do not involve just one angiosome; direct revascularization is not invariably technically feasible; and the arterial system of the foot includes numerous collateral vessels that connect the systems of the major arterial trunks. Therefore, indirect revascularization also should improve perfusion of the involved tissue. Kret et al. reported that due to technical factors direct revascularization was possible in just 50.9% of their series of CLI patients [20]. Troisi et al. published similar findings, i.e. direct revascularization was technically feasible in 59.1% of their CLI patients. According to Troisi et al., direct angiosome-guided revascularization is not a predictor of wound healing in diabetic patients with CLI undergoing an endoscopic procedure. Pedal arch patency is of key importance for wound healing and limb salvage [19]. Rashid et al. made a similar observation for CLI patients undergoing distal bypass [21]. Varela et al. demonstrated that indirect reperfusion through collateral vessels that remained patent (mostly the pedal arch and distal peroneal branches) gave similar results to those obtained with direct revascularization [22]. Finally, the success of tissue reperfusion in the ulcer area also depends on the status of microcirculation, which in diabetic patients, especially those with coexisting chronic renal disease, is severely impaired due to microangiopathy [23].

In conclusion, although knowledge of the principles guiding revascularization procedures is mandatory, a dogmatic approach is not advised. Very often it is the patient's vascular status that guides the choice of reperfusion procedure.

Technical aspects of percutaneous balloon angioplasty of infrapopliteal arteries

At present, percutaneous transluminal angioplasty is the standard, most commonly performed procedure, considered in most cases a technique of choice for revascularization of infrapopliteal arteries [24, 25]. An ipsilateral common femoral approach is typically used. The puncture entry site is made on the common femoral artery or the proximal segment of the superficial femoral artery on the ipsilateral side. Ultrasound can be used during artery puncture to select the optimal site for a sheath placement. Insertion of a 40–45 cm sheath into the popliteal artery using the ipsilateral approach maximally shortens the distance to the target arteries and provides the best support for the pair guidewire-catheter. Under special circumstances, e.g. in very obese patients or in those with coexisting atherosclerotic lesions in the iliofemoral segment, a crossover technique from the contralateral femoral artery is used for access. Longer endovascular devices are then required, and surgical manipulation below the knee is considerably more difficult.

Often, to recanalize infrapopliteal arteries an additional retrograde access is needed through the distal arteries (dorsalis pedis, distal segments of the posterior tibial artery or the peroneal artery). Ultrasound-guided puncture is then used. Also, fluoroscopic guidance may be used, especially with densely calcified lesions. Peripheral access is made with a dedicated micropuncture set or the sheathless approach is used – a bareback guidewire as the only support for a balloon catheter. More experienced centres use a retrograde approach to gain access through even thinner vessels such as arteries of the midfoot or the plantar arteries, lateral or medial.

The patient is systemically heparinized immediately after the sheath has been placed (intra-arterial unfractionated heparin 5000 IU). The effectiveness of peripheral interventions is enhanced by intra-arterial vasodilators such as verapamil (1–2.5 mg), nitroglycerin (100–200 mcg), or papaverine (5–10 mg). Pre-procedurally the patient receives dual loading antiplatelet therapy, usually acetylsalicylic acid and clopidogrel.

Next, the arteries in the leg are assessed using imaging studies – often selective angiography of infrapopliteal arteries. In some centres, imaging studies are performed on the day preceding the intervention, to limit the patient's exposure to radiation and the amount of contrast medium given at one time, to plan the revascularization strategy to be used, and to select appropriate endovascular devices. The ipsilateral oblique projection is used in imaging the proximal and middle segments of infrapopliteal arteries while the contralateral oblique projection is used to identify the origin of the anterior tibial artery. The contralateral oblique projection is also used to visualize the distal segments of infrapopliteal arteries and arteries of the foot in position of abduction. The posteroanterior projection is optimal for visualizing the pedal arch with the arteries of the midfoot.

Intraluminal revascularization is the approach of choice although fibrocalcific caps at the 2 ends of an atherosclerotic lesion may prove a technical problem because it is often difficult to pass through such occluded segment via this approach. Nowadays, a wider range of special catheters that facilitate recanalization are available, including 2.6 F microcatheters. These are braided catheters that provide improved guidewire support while a hydrophilic coating facilitates crossing the lesion.

The choice of guidewires specifically designed for lower extremity artery angioplasty is also broad. Nowadays, 0.018" and 0.014" guidewires are used in most procedures, and 0.035" guidewires only occasionally because their calibre is too large. Guidewires differ in their constructive properties, coating, and characteristics of the body and the tip. These factors determine the stiffness and the degree of pressure possible with a given type of guidewire and whether the guidewire tip can be shaped. With stiffer guidewires' crossing of the lesion and the delivery of the balloon catheter may be easier, but they are less useful in tortuous vessels and increase the risk for extravasation. At the start of the procedure, a medium-stiff 0.014" guidewire is used and crossing of the lesion is attempted with the "drilling" technique, i.e. the guidewire is rotated alternately clockwise and counter-clockwise with only a slight pressure along the long axis. When this fails, the previous guidewire may be exchanged for a stiffer 0.014" guidewire or a 0.018" guidewire. When the guidewire passes into the subintimal space it should left there and a second guidewire advanced (the parallel guidewire method) (Table 3).

When an intraluminal procedure is ineffective, a subintimal approach to the lesion may be attempted, mostly using 0.018" guidewires. The subintimal space is entered at the level of the proximal cap, and a short loop is created at the tip of the

Table 3. A selection of 0.014″ guidewires designed for angioplasty of below-the-knee arteries

Manufacturer	Model	Level of support	Tip load [g]	Main use
Abbott Vascular	Command	Low	2.8	Navigation/stenoses
Abbott Vascular	Command ES	Moderate	3.5	Navigation/stenoses/short-length occlusions
Abbott Vascular	Winn 40	Moderate	5.1	Occlusions
Abbott Vascular	Winn 80	Moderate	11.3	Occlusions
	Winn 200 T	Moderate	14.3	Occlusions
Abbott Vascular	Spartacore	High	1.0–1.1	Balloon catheter platform
Asahi	Gladius ES	High	3	Navigation /stenoses/short-length occlusions
Asahi	Halberd	Moderate	12	Occlusions/calcification
Asahi	Regalia XS 1.0	Low	1.0	Vascular tortuosity/collateral access/ subintimal recanalization
Asahi	Asato XS 20	Moderate	20	Crossing highly calcified lesions
Boston Scientific	V14	High	3.6	Navigation/stenoses
Boston Scientific	Victory 14	Moderate	12, 18, 25, 30	Crossing highly calcified lesions
Boston Scientific	Platinum Plus	High	7	Balloon catheter platform/stenoses
Cook Medical	Approach CTO	Moderate	6, 12, 18, 25	Stenoses/occlusions
Terumo	Glidewire Advantage	High	–	Balloon catheter platform/stenoses

guidewire, which is then further advanced with the aid of a support or balloon catheter. After the guidewire has successfully passed the occlusion, it should re-enter the true lumen. The re-entry is often technically challenging, especially when the vessel wall is highly calcified. One of the challenges is to avoid injury to the patent vessel distant to the occlusion.

Advancing a guidewire through the lesion in the antegrade direction is unsuccessful in approximately 10–20% of interventions, and the retrograde approach is then attempted. This is achieved via an additional peripheral access. Artery puncture is performed with a 21 G needle, and a 0.018″ guidewire is usually used to cross the lesion. Retrograde recanalization may be achieved in either an intraluminal procedure or using the SAFARI technique (subintimal arterial flossing with antegrade-retrograde intervention). The guidewire introduced in the retrograde direction is retrieved with a snare loop via a proximal access or by its insertion into the antegrade catheter (the *rendez vous* technique). Balloon angioplasty is then performed typically using the proximal sheath. After the sheath removal, haemostasis of the distal access is achieved employing prolonged balloon inflation at the access site.

Also, when the collateral vessels are patent, a guidewire and a catheter may be advanced into peripheral vessels through a collateral channel and a balloon angioplasty procedure performed.

When the guidewire has traversed the stenosis or occlusive lesion, balloon angioplasty is done. It may be plain old balloon angioplasty performed using a wide selection of low-profile, high-pressure balloon catheters varying in length and diameter. The ideal duration of balloon inflation during below-the-knee artery angioplasty has not been identified in clinical trials. Published reports suggest that a prolonged inflation time (180 seconds) is preferable to a shorter dilation time (30 seconds) [26]. In clinical practice, co-axial catheters are more commonly used as they provide improved support and easier crossing of the lesion than monorail catheters. Tapered balloons with a decremental diameter (a difference of 0.5 mm between the proximal and distal diameters) have been designed for angioplasty of long-segmented lesions. Also available is the cutting catheter with microsurgical blades (atheromes) bonded longitudinally to its surface for controlled incisions of the atherosclerotic lesion during balloon inflation. The device is used mostly for highly calcified or fibrous lesions refractory to conventional balloon angioplasty and prone to elastic recoil, or a rebound of a vessel wall after angioplasty.

The effectiveness of balloon angioplasty as the essential technique for revascularization of below-the-knee arteries in diabetic patients has been confirmed by the outcomes, which include reduced rates of amputation [27–29]. One-year restenosis rates remain high and are related to the length of the lesion and the degree of stenosis. Ferraresi et al. reported target vessel restenosis one year after revascularization procedure in 42%

of their patients (35% of the stenosis group and 53% of the occlusion group) [27]. However, the period of improved tissue perfusion, even if limited, allows for infection control and healing of the ulcer. When the wound has healed, the subsequent restenosis or re-occlusion are often asymptomatic. Sadek et al. reported a limb salvage rate of 81% one year after revascularization and primary patency rate of just 50% [28]. Similarly, Park et al. reported a limb salvage rate of 90% and primary patency rate of 59% [29]. Drug-eluting balloons appear to be promising in terms of limiting the amount of restenosis, but further multicentre randomized clinical trials are needed to assess their long-term efficacy and safety [30–32].

Conclusions

As the prevalence and incidence of diabetes continue to increase, CLI in diabetic patients emerges as a growing clinical problem. As shown above, the course of critical ischaemia in patients with diabetes differs in a number of features from that in patients without diabetes. However, with advances in technology, technically complex endovascular interventions become feasible, which is reflected in improved limb salvage. The continuing education and growing experience of vascular surgeons and interventional radiologists as well as adequate funding for the health sector seem to be of key importance for successful resolution of this very challenging and dramatic heath problem, which not only has a negative impact on health-related quality of life, but also generates huge indirect costs.

Conflict of interest

The authors declare no conflict of interest.

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