14 Peripheral Vascular Disease and Endovascular Therapy in Singapore

T.Y. Tang, S. Kum, P. Ho, and Y.K. Tan

Introduction

Peripheral arterial disease (PAD) is a significant complication of diabetes mellitus and accounts for the majority of amputations among these patients [1]. A major lower limb amputation due to complications from diabetes occurs once every 30 s worldwide. In Singapore, it is estimated that about 1500 major lower limb amputations take place a year (approximately four per day). In addition, PAD is a manifestation of systemic atherosclerosis and is associated with increased risk of mortality and ischaemic events [2]. Despite its associations with increased morbidity and mortality, PAD is under-diagnosed and under-treated in the general Singaporean population. Patients with diabetes have unique problems with PAD, as the disease appears to affect predominantly the tibial blood vessels where open bypass surgery is often difficult with generally poor results and angioplasty generally the better option. Furthermore, pain is often not prominent due to superimposed neuropathy, and this puts them at risk of seeking medical attention only in advanced stages when there is a significant wound to heal [3]. This in turn leads to increased costly consequences such as hospitalisation for ulcers, revascularisation, amputation, need for rehabilitation and loss of employability and income.

The prevalence of PAD among patients with diabetes in the Western population ranges from 16 to 22 % [4, 5]. Comparatively, less is known about PAD among Asian populations although some studies have found lower prevalence rates ranging from 6 to 10 % [6, 7]. The Singapore REACH registry [8] reported that PAD is estimated to affect about 8.1 % of the local population, and this percentage increases with age. The incidence of PAD is expected to increase in an aging population with advancing longevity. Although this disparity in PAD prevalence between Asian and Western populations may well be true, it is likely to be attributed to underdiagnosis of this condition among Asian diabetic patients.

Narayanan et al. [9] measured the prevalence and associated factors of PAD in diabetic patients from multi-ethnic communities in Singapore. They systematically sampled 697 patients from the 3607 patients with diabetes who visited nine polyclinics during the study period, giving an overall sampling rate of 19.3 %. The population consisted of 67.0 % Chinese, 15.2 % Malays, 16.1 % Indians and 1.7 % of other ethnic groups. The prevalence of PAD among the patients with diabetes was 15.2 %, with significant differences among Chinese, Malays and Indians. Among Chinese patients, 12.6 % had PAD, compared to 17.9 % among Indians and 22.8 % among Malays.

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Patients with PAD tended to be older (66.8 vs 59.1 years of age; $P<0.001$) and had longer duration of diabetes (13.9 vs 9.8 years; $P<0.001$). From a prevalence of nearly 5 % in those below 40 years of age, the rates increased across the age groups, with nearly one in three patients above 70 years of age having PAD. Less than 10 % of patients with duration of diabetes less than 6 years had PAD, but prevalence increased with increasing duration, reaching nearly 25 % in those who had diabetes for more than 20 years. Diabetic patients with PAD were more likely to have ischaemic heart disease, stroke, peripheral neuropathy, nephropathy and retinopathy compared to patients without PAD. Factors associated with PAD in a multivariate model found increasing age, Malay ethnicity, having low serum HDL-cholesterol and insulin treatment to be factors significantly associated with an increased prevalence of PAD in this cross-sectional study. The prevalence of PVD in another Singaporean- based study was found to be 4.3 % [10]. This large, multi-ethnic, Asian population based cohort found that PAD was commonest in Indians, followed by Malays and Chinese. Apart from traditional vascular risk factors, pulse pressure, renal impairment and past history of stroke were important determinants of PAD.

Distribution of PVD in Asians

To date, there is limited data on the arterial disease distribution in diabetic patients in the Asian population. Similar European studies have shown that the arterial disease pattern in diabetics tend to be confined to the infra-popliteal vessels.

A retrospective study of consecutive diabetic patients with critical lower limb ischaemia who underwent endovascular revascularization over a 6-month period in Changi General Hospital (CGH) was carried out [11]. Fifty-seven subjects were enrolled in the study. The mean age of patients was 70 years old with a male predominance (60 %). Fifty-eight percent of the subjects enrolled were Chinese followed by Malay (30 %), Indian (7 %) and others (5 %). Of all co-morbidities, 35 % of subjects had end stage renal failure. Seventy-six percent of subjects had major tissue loss (Rutherford Grade IV and V). Arterial disease was predominantly confined to the infra-apopliteal vessels with significant percentage of patients having long segment occlusions in this group (occlusion > 50 % of vessel length) (See Figs. 14.1 and 14.2). There was also significant disease involving the pedal vessels as well (dorsalis pedis and plantar artery). This study concluded that infrapopliteal vessels were more

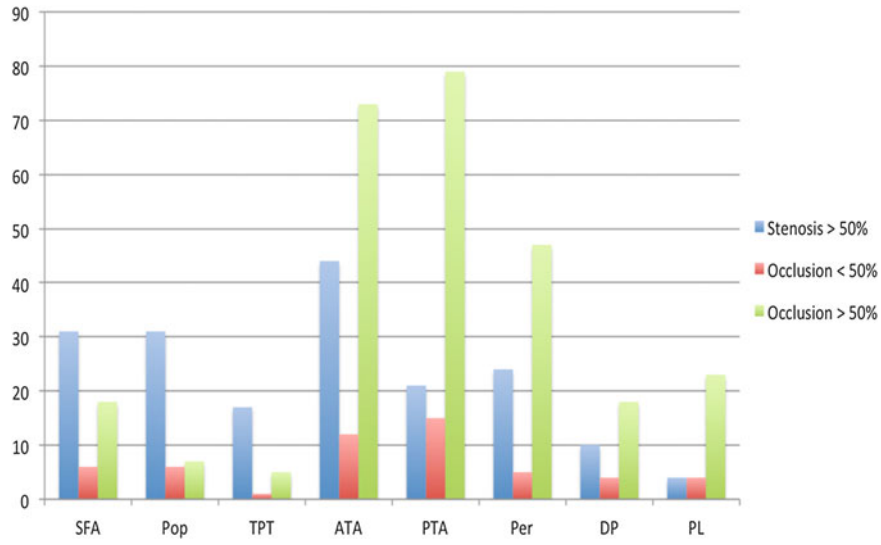

Fig. 14.1 Categorization of arterial disease pattern according to individual vessels

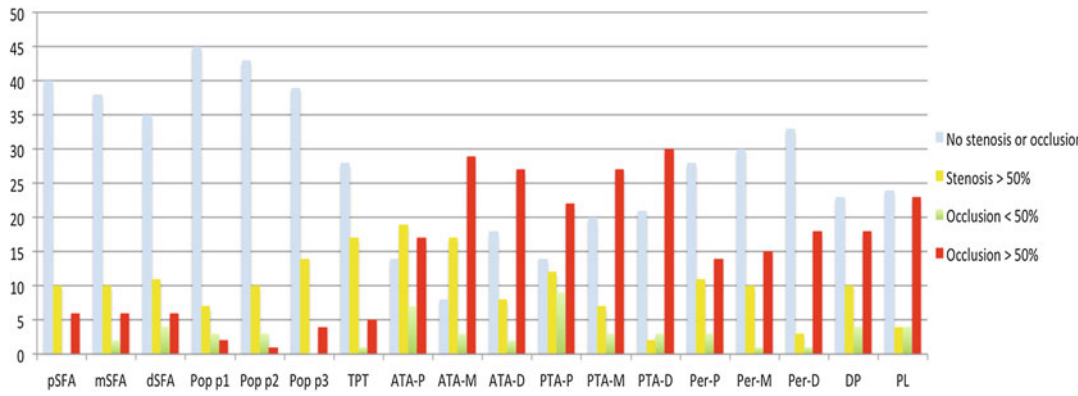

Fig. 14.2 Categorization of arterial disease pattern according to individual vessels with further subdivisions of each vessel into proximal, middle and distal segments

commonly diseased in diabetics in the Asian population and tend to present with long segment occlusions. As such, this would pose a higher technical difficulty in terms of revascularization, be it endovascular or open bypass procedures, where there would be limited availability of appropriate distal arteries to bypass to.

Intervention for PAD

One of the foremost programs launched by the Ministry of Health in studying the treatment of patients with PAD was conducted in Tan Tock Sing Hospital (TTSH) by the Vascular Surgery team. The LEAP (Lower Amputation Prevention) for Life program was first proposed by the late Dr Alexandre Chao who successfully managed to institute a 4 year program in TTSH. The program began in 2001 and was completed in 2005. During this period, a total of 413 patients were enrolled. These patients were assessed and treated with a combination of modalities including bypass surgery, limb angioplasty, pneumatic compression therapy or hyperbaric oxygen therapy. Early analysis of the results has shown successful prevention of lower limb amputations with successful limb salvage in 81.3 % of patients. Patients have also managed to retain their functional status following successful intervention, with at least 80 % of patients being able to resume their premorbid daily activities.

Endovascular Therapy

The trend of clinicians to adopt endovascular interventions for PAD has increased more than threefold in the past decade [12]. Many researchers suggested that endovascular intervention could be the first line of treatment in PAD patients [13, 14]. They indicated that endovascular intervention is safe and provides acceptable clinical improvements. The prevalence of endovascular therapy for PAD is moderate and rising in Singapore. Greater awareness by patient and referring physicians in addition to improvements in endovascular proficiencies continue to drive demand for endovascular solutions in Singapore. Disease-specific devices, relatively open regulatory environment allow today's physicians to offer cutting edge technologies to patients who otherwise could not have been treated by endotherapy. Vascular surgeons are increasingly adopting an endovascular-first approach, which probably accounts for a large proportion of the rising trend because our pool of patients is mostly elderly with multiple co-morbidities. Surgical risk profile is high. Secondly, below the knee disease is the predominant lesion in our patient population. Tibial bypass usually lands on only one target distal vessel, whereas endovascular therapy can open up as many tibial arteries as feasible, depending on the disease status and clinician's skill, which may in turn result in better revascularization to the foot and toes. Patients'

preference of a minimally invasive therapy also makes endovascular intervention a more acceptable treatment option. Asian patients are in our opinion particularly adverse to an amputation (minor or major) due to religious and cultural beliefs. Some patients believe they should go to their maker with intact body/appendages. Older patients are generally adverse to a big incision (e.g. a bypass). Endovascular Therapy is therefore a safe and attractive option for both the physician and elderly patients. However, some Asian patients are adverse to having metallic implants such as stents.

May et al. [15] reviewed the outcome of PAD patients managed with an endovascular first approach for revascularization in a tertiary referral centre in Singapore. Over a 2-year period, revascularization procedures were performed for 202 PAD patients with 229 symptomatic limbs. Angiogram was performed in all patients except those contraindicated for contrast agent. Angioplasty revascularization was carried out on the same setting whenever feasible based on the angiogram findings. Bypass surgery was performed in patients with arterial condition not feasible for endovascular intervention or in those with unsatisfactory revascularization after endovascular treatment. Among 229 symptomatic limbs, 194 limbs presented with critical ischaemia and 35 with severe claudication. Endovascular intervention was successfully performed in 198 limbs (86 %). Bypass surgery was required in 31 (15 %) patients with two of them had sequential endovascular intervention performed due to multi-level arterial involvement. Another 16 (8 %) patients required a bypass after endovascular intervention due to unsatisfactory wound healing. All cause 30 day mortality was 5.2 %. The Kaplan-Meier estimated survival and amputation free survival were 80 % and 75.5 % at 1 year and, 73 % and 57.6 % at 2 years respectively. They concluded that satisfactory limb salvage rate can be achieved in PAD patients managed with an endovascular first approach. The same group also investigated patients with intra-procedural acute thrombosis (IPAT) due to emboli or thrombosis during an endovascular salvage procedure. Indian ethnicity, in-stent occlusion and prior IPAT are associated with IPAT occurrence during endovascular interventions. Despite successful salvage, patients with IPAT appear to have poorer post-procedural runoff and are more likely to require subsequent endovascular procedures or arterial bypass when compared to patients from the control group. However, major amputation rates, overall survival and amputation –free survival are not significantly worse in IPAT patients [16].

Device Availability, Reimbursement and Training

Singapore is home to regional headquarters of several medical device companies. Devices from various companies are readily available and competition within each class of device is stiff, pushing companies to be more performance and evidence-based driven. In addition, sale of devices based on transparency and meritocracy allow companies to compete on a more level playing field. Singapore is a financial and medical bell weather for the region so this encourages companies to continue having a presence here. The regulatory environment is considered both friendly and competitive currently.

Reimbursement for medical devices is certainly a major factor all around the world. Patients still have to fork out from their pockets substantial amount of cash for devices, although the situation is improving with better conditions and subsidy given from the government MediShield program. We believe that patients will be willing to pay for the devices if a physician is able to communicate the benefits of endovascular therapy over open surgery and is competently able to deliver good results. Patients with private insurance are however well covered for medical devices. Regardless, in a cost conscious environment, knowledge of the limitations and strengths of each device will ensure physicians adopt a rational use of devices.

Endovascular training is an on-going lifelong process even for experienced physicians as long as medical device companies continue to innovate.

Training is mainly by hands-on apprenticeship, although the use of endovascular trainers is certainly helpful. We regularly run live case workshops in our hybrid suite at CGH to help train local and regional physicians across all disciplines to adopt these techniques.

Strategies for Dealing with Short Focal Lesions, Long Lesions, Calcified Lesions, CTOs, In Stent Restenosis (ISR) in the Superficial Femoral Artery and Claudicants

The following is an algorithm for treating the above-named lesions and is based on the personal experiences of the authors, treating a heavy cohort of multi ethnic patients with PAD in Singapore.

Short, Focal Lesions

There is good evidence for utilising drug eluting balloons (DEBs) for short focal SFA lesions and this is the strategy we would generally employ. If the mechanical recoil or dissection is severe after pre-dilatation, we may consider a drug eluting stent (DES).

Long Lesions

These are the common real world lesions. The patency is generally poor for plain old balloon angioplasty (POBA) and although better with stents, in stent restenosis (ISR) continue to pose a real problem. Very often, we end up sub-intimal in a long Complete Total Occlusion (CTO) and in a calcified vessel, stents are the only practical alternative to provide a mechanical solution to what will likely be a heavily dissected vessel. We try to limit the length of stents as much as we can. Scoring Chocolate balloons (QT Vascular) are occasionally used to limit the severity of dissection. If the mechanical result is good, we would consider DEBs although the evidence for long lesions is mostly registry-based.

In the occasional long diffuse stenotic lesions (especially calcified ones), we would like to consider the patient for Rotational Atherectomy (Jetstream) to initially debulk the lesion and then to line it with a DEB. This is to avoid dissection and then expose the vessel wall to the Paclitaxel drug. The results from the DEFINITIVE AR Study (REF) are encouraging for directional atherectomy in combination with DEBs and we would like to think that this can be extrapolated for Rotational Atherectomy. We are hesitant to do atherectomy in a long CTO where the wire is frequently in the subintimal plane because the risk of perforation is high.

Calcified Lesions

This is often a stubborn problem and the solutions are mainly mechanically based. Lesions that respond poorly to POBA need to be stented with dedicated stents that can deliver high radial resistive forces. We have employed the PIERCE technique (Percutaneous Direct Needle Puncture of Calcified Plaque) [17] in the SFA and BTK with good results. It is safe and improves the compliance of the vessel for a better POBA or stent result in the event high pressure POBA not working. We occasionally use it during vessel preparation before stenting.

CTOs

POBA has poor results and adjunctive techniques are employed to improve acute and long term results. As per long lesions above.

In-Stent Restenosis (ISR)

With growing utilisation of stents ISR has been a real problem and the results of POBA are poor. For symptomatic ISRs or occlusions, we employ DEBs with or without Rotarex thrombectomy and there are good results from several registries. We generally avoid covered stents as our SFAs are generally smaller in Asia (5 mm) and there is

concern about stent thrombosis should we have a stent in stent strategy. It is frustrating that heparin coated covered stents are not available currently in Singapore.

Below Knee Disease and Bio-Absorbable Vascular Scaffolds (BVS)

Below knee diseases (BTK) are challenging to treat. This is due to the extent of burden of disease, particularly in diabetic and high post-PTA restenosis rates.

With advances in drug eluting technologies, prospective clinical trials in relatively small CLI patient cohorts, tibial vessel drug-eluting balloon (DEB) angioplasty was associated with significantly reduced restenosis rates and late lumen loss (LLL) [18]. However, DEBs do not provide the mechanical advantage of endo-luminal stents. Stenting of infrapopliteal lesions are often limited by a relatively high restenosis rate and subsequent late in-stent thrombosis. The bioabsorbable stent (BVS) is a novel development that provides initial scaffolding support, elutes anti-proliferative drugs to prevent vessel restenosis and reabsorbs subsequently to reduce risk of in stent thrombosis. It hopes to address issues with pre-existing stents and promises to be the next frontier in endovascular revascularisation.

At CGH, we have investigated the early outcomes, efficacy and safety of a biorebsorbable stent (ABSORB BVS) in patients with below knee critical limb ischaemia. A case series of 13 patients with median age 67 (range 46–89) who underwent stenting of below knee arterial diseases with Bioabsorbable Everolimus Eluting Bioresorbable Vascular Scaffold System developed by Abbott Vascular (Abbott, Illinois, USA). The primary outcomes measured were stent patency, target lesion revascularization (TLR) and limb salvage rates. Thirty BVS were inserted for 14 below knee lesions. The median length of the lesions was 25 mm (range 10–70). Majority of patients has significant critical limb ischemia (Rutherford 5–6). Technical success was 100 %. Six months vessel patency, TLR and limb salvage rates were 75, 8.3 and 91.7 % respectively. There were no procedure related complications or deaths. Our study shows that BVS for below knee diseases have fairly good early outcomes, is safe and technically feasible. Longer follow-up and more rigorous clinical trials for BVS are required to determine its clinical benefits over pre-existing stents.

Claudicants

Claudicants have a good life expectancy and low risk for limb loss. Patency is required to keep them symptom free. In the absence of a good long term solution for In-Stent Occlusions/restenosis, we like to avoid stents as much as possible. We would generally consider DEBs with bailout stenting for short lesions (as evidenced by the trials on the SFA by Medtronic and Lutonix), which give us good freedom from TLRs. For longer lesions, DEBs and bailout stenting is employed although the majority of the evidence is registry-based and we have had good results with this strategy. The caveat is that after pre-dilatation, the mechanical result has to be reasonably good (i.e. no severe recoil or dissection). The lesions that have a mechanical predominant problem are probably best served with dedicated new generation stent with low Chronic Outward Force but high Radial Resistive Force. The combination concept of deliberate DEB and Stenting is interesting and we await the results earnestly

The strategy is in contrast to CLI patients who need maximum effort for limb salvage (a Femoral -Popliteal Bypass equivalent in the SFA). These patients have a limited life expectancy and may not be symptomatic from a SFA ISR. Lesion for lesion, we tend to stent these as compared to the claudicants.

Deep Venous Arterialization

It is common to see a presentation of a so-called "*desert foot*" without discernible targets for bypass or intervention. Many patients have already undergone multiple interventions. This is coined the "no-option" end-stage CLI patient. Stem cell therapy may offer some promise but is still in a relatively early phase of evaluation.

Deep venous arterialization (DVA) is not a new concept. It involves shunting arterial blood to the deep veins. Early surgical attempts and more recent surgical series reported good safety and clinical outcomes [19, 20]. These surgical approaches were plagued by valves, which are a hindrance to blood flow and would need to be made incompetent. In addition, numerous draining venous collaterals would "steal" the blood flow to the extremity. At CGH, we sought to implement this concept of DVA using a completely percutaneous approach (Fig. 14.3), percutaneous deep venous arterialization (PDVA), and have achieved some initial angiographic and clinical success.

This proof-of-concept and safety study was carried out in CGH in Singapore. This was a pilot, prospective, open-label, single-center, single-arm study under the auspices of our Institutional Review Board.

All patients were deemed "end stage" with no remaining conventional open or endovascular options as verified independently by another vascular surgeon or interventionist. Extensive bench, in vivo animal, and cadaver studies were successfully performed prior to the study.

The inclusion criteria allowed for enrolment of adult patients at imminent risk of major amputation as a result of CLI. These included Rutherford class 5 or 6 patients with an absence of a reasonable target vessel for bypass or endovascular intervention or severely diseased plantar arch or digital vessels.

Seven patients were included in the study with the following conditions: five chronic non-healing wounds/gangrene, one severe rest pain, and one severe rest pain and chronic non-healing wound. All patients had diabetes and were between the age of 49 and 94 years. Five of the seven patients had PDVA with the LimFlow device (MD Start).

The primary objective of the investigation was to determine the safety of PDVA. Secondary objectives included clinical efficacy at 6 months with outcome measures such as thermal measurement, limb oxygenations, clinical observation, and wound healing during the 6-month follow-up period.

Subjective and objective markers of perfusion were evaluated with infrared thermography (FLIR, FLIR Systems), transcutaneous oximetry measurements, and wound healing time.

The LimFlow device consists of a 7-F arterial catheter, a 5-F venous catheter, and a console to facilitate the crossing procedure with a needle. An antegrade arterial 7-F sheath and a retrograde posterior tibial vein 5-F sheath are both placed under ultrasound guidance.

Control angiography is performed to show the crossover point, the area where a needle from

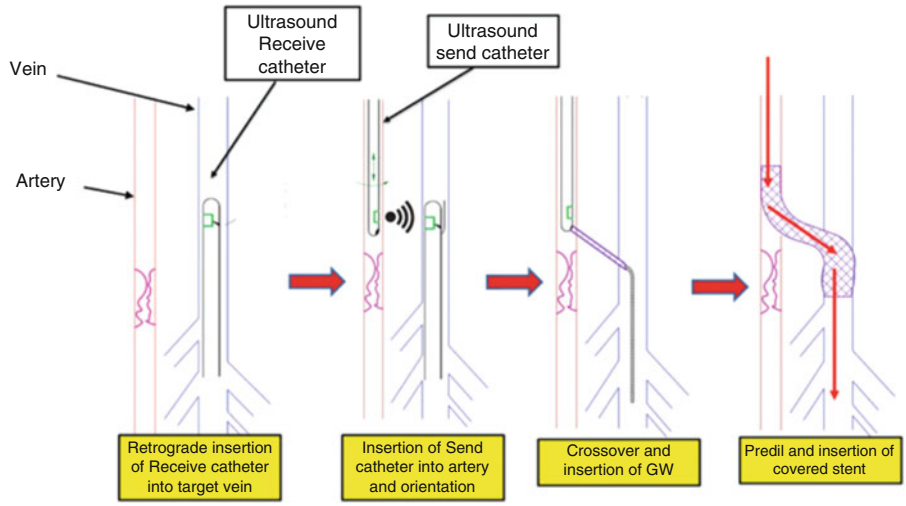

Fig. 14.3 Overview of the LimFlow approach to percutaneous deep venous arterialization

the arterial catheter is anticipated to traverse into the vein. The arterial and venous catheters are aligned with a proprietary ultrasonic system. A 0.014-in. guidewire is then driven across the crossover point and into the retrograde sheath, supported by a 3- × 40-mm balloon, which is also used to predilate the arteriovenous fistula. The 0.014-in. guidewire is then exchanged for a 0.018-in. guidewire over a 0.018-in. support catheter and used to cross the valves. A proprietary reversed valvulotome is used to disrupt the valves, in order to allow uninhibited proximal-to-distal blood flow.

The length of posterior tibial vein up to the patent posterior tibial artery is lined with a covered stent, which serves to cover the venous collaterals and also disrupt blood flow to the proximal valves. In addition, it guarantees a large conduit for blood flow by forcefully rupturing the proximal veins.

Pre- and post-procedure results of angiography using an iFlow postprocessing program (Siemens) are shown in Fig. 14.4a, b. The post-procedure angiogram demonstrates rapid arrival of contrast from the time of acquisition of the DSA (coded yellow/red) (Fig. 14.4b). This is compared to the pre-procedure iFlow (Fig. 14.4a). An angiographic "blush" is also seen at the edge of the wound, as well as multiple collateral vessels at the foot that serve as runoffs. Skin temperature also improved, as seen on FLIR thermography (Fig. 14.5).

Clinical success was also seen in another patient, with wound healing after 115 days and the resolution of opioid-dependent rest pain immediately after the procedure (Fig. 14.6). Increased transcutaneous oximetry levels were seen in four out of the five patients who underwent PDVA with LimFlow. Of the six patients with wounds, four healed, one is still healing, and one had to undergo amputation for systemic infection (the patient had heel gangrene with osteomyelitis but had evidence of good perfusion and granulation).

Percutaneous DVA represents a new concept in perfusing the foot by routing blood into the deep venous circulation. We were able to perform this safely, with no major adverse events observed within the first 30 days.

From our initial experience with LimFlow, the crossing was easily performed, and the valvulotome assisted in disrupting the valves and diverted blood to the wound bed, allowing us to achieve the goals of wound healing, resolution of rest pain, and a rise in transcutaneous oximetry. This technique represents a novel way to percutaneously treat the "no-option" end-stage CLI patient. It marries the advantage of surgical DVA with

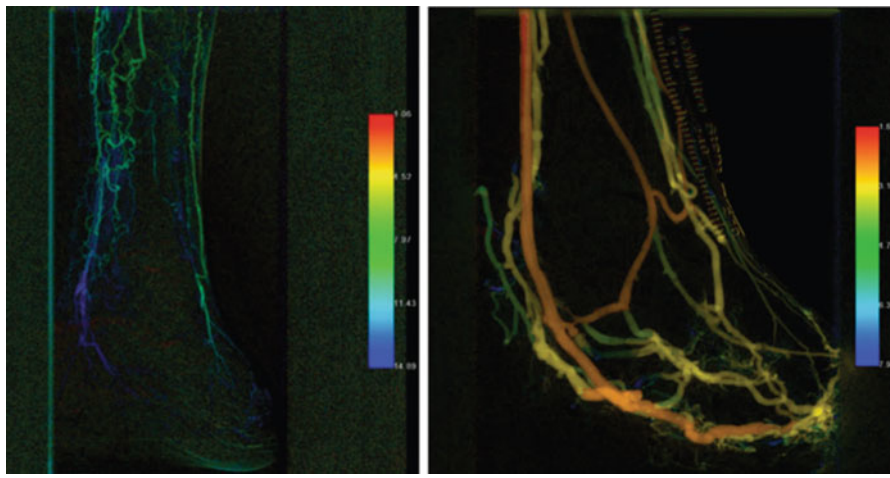

Fig. 14.4 Preprocedure (**a**) and postprocedure (**b**) angiograms using iFlow. Note the angiographic blush at the wound on the extreme lower right

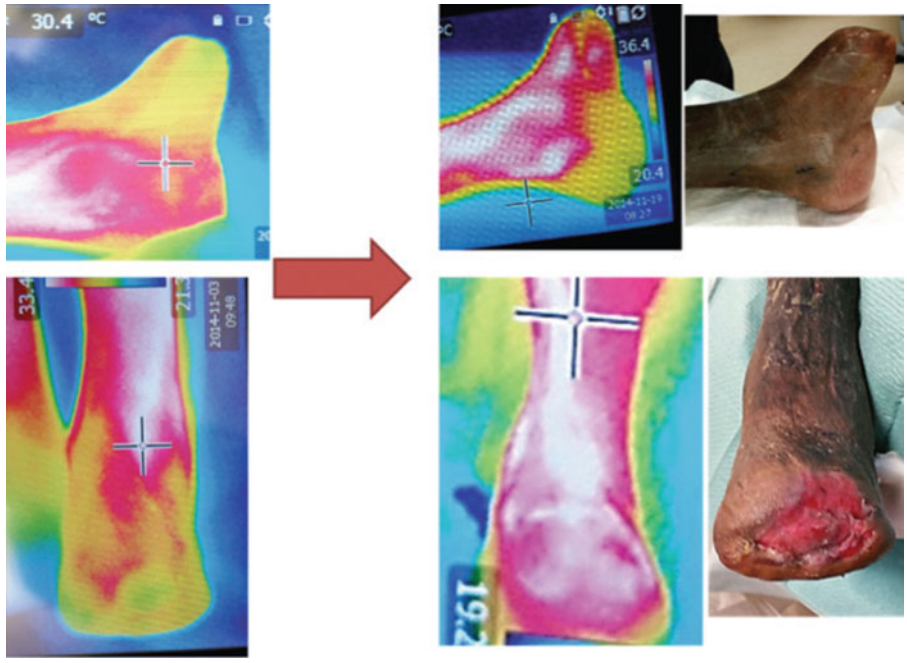

Fig. 14.5 Preprocedure versus postprocedure FLIR thermography

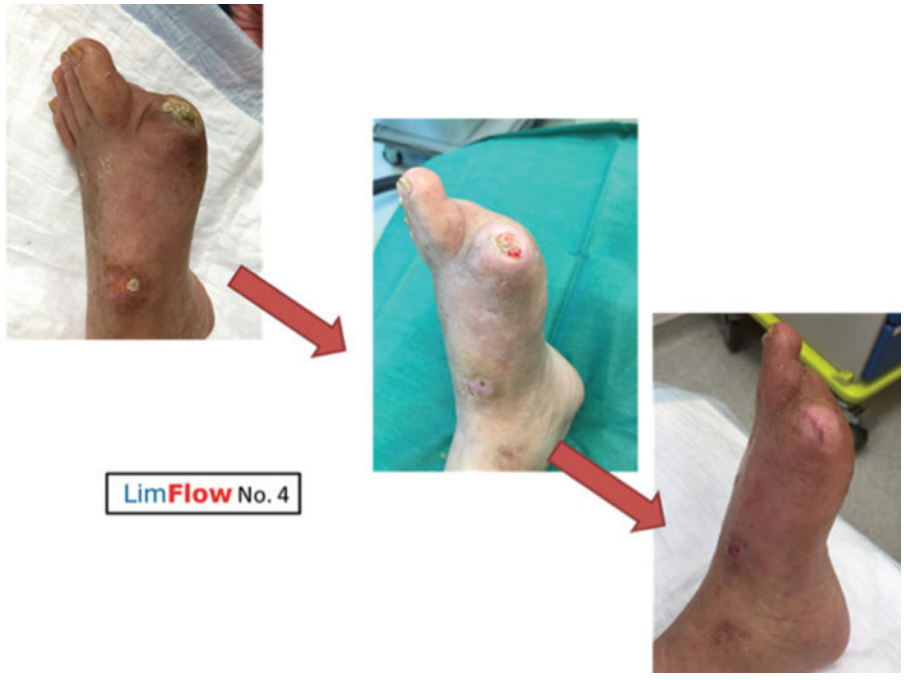

Fig. 14.6 An example of wound healing in a patient who underwent percutaneous deep venous arterialization using LimFlow

those of a minimally invasive procedure, aided by the LimFlow device.

Challenges clearly remain in the treatment of CLI. Wound healing still demands a multiprong approach with revascularization, control of infection, and meticulous wound care. The device is still undergoing improvements, and we continue to grow our experience of operating in the venous environment of the leg.

A CE Mark study is currently underway in Singapore, Germany, and Italy. A pre-investigational device exemption application has been submitted to the US Food and Drug Administration and accepted into an early feasibility study program.

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