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Angiosome perfusion of the foot: An old theory or a new issue?

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ABSTRACT

The angiosome concept of foot perfusion was conceived based on anatomical studies of arterial circulation and used for planning surgical procedures, tissue reconstruction, and amputation. Its application is relevant in diabetic patients with critical limb ischemia and nonhealing foot ulcer or amputation. An understanding of foot angiosome anatomy is useful for predicting healing and planning arterial revascularization. A review of the literature, including the most recent systematic reviews and meta-analyses, indicates improved wound healing is achieved when the angiosome concept is followed. The greatest value of angiosome-based revascularization is in patients with lesion(s) limited to a single angiosome, or to achieve optimal healing of amputation sites. Future research should focus on proper identification of (imaging) modalities to determine the hemodynamic and functional changes before and after revascularization, thus identifying the "real" angiosome and directing optimal therapy.

1. Introduction

The incidence of critical limb ischemia (CLI) is increasing, and diabetic patients are especially prone to developing ischemic and neuro-ischemic foot ulcers. Twelve to 25% of diabetic patients may develop a foot lesion over time [1]. Diabetic patients often present with more extensive tissue loss compared to non-diabetic patients [2]. The importance of revascularization of the lower limb in patients with CLI has been well established, and expedited revascularization is mandatory once an ischemic foot ulcer is detected. Although there is still a role for surgical bypass, over the last several decades the use of endovascular techniques has become more frequent. This development has been made possible by the evolution of endovascular devices and operator skills. The less-invasive endovascular approach is the preferred treatment method, especially in the frail diabetic patient with multiple comorbidities [3]. Incisional wound healing in diabetic patients can also be problematic [4]. In both open and endovascular revascularization there is a clear difference of approach in patients with CLI caused by inflow disease (iliac, femoral, and popliteal disease) and those with (additional) infrapopliteal involvement. Whereas in above-the-knee disease, it is clear that flow in the stenotic or occluded segment needs to be re-established, in below-the-knee (BTK) disease, potentially three vessels can be revascularized, and this poses a therapeutic dilemma (especially for open revascularization). Choosing the correct target for revascularization can present a critical, complex issue in challenging cases, especially when multilevel arterial disease is present [1]. Revascularization can be accomplished by using two approaches: "complete" revascularization (one vessel is better than none, two to three vessels are better than one) or "wound-related" revascularization [1]. With CLI, the healing of an ulcer is blood-flow–dependent and the goal of treatment should be to get the best

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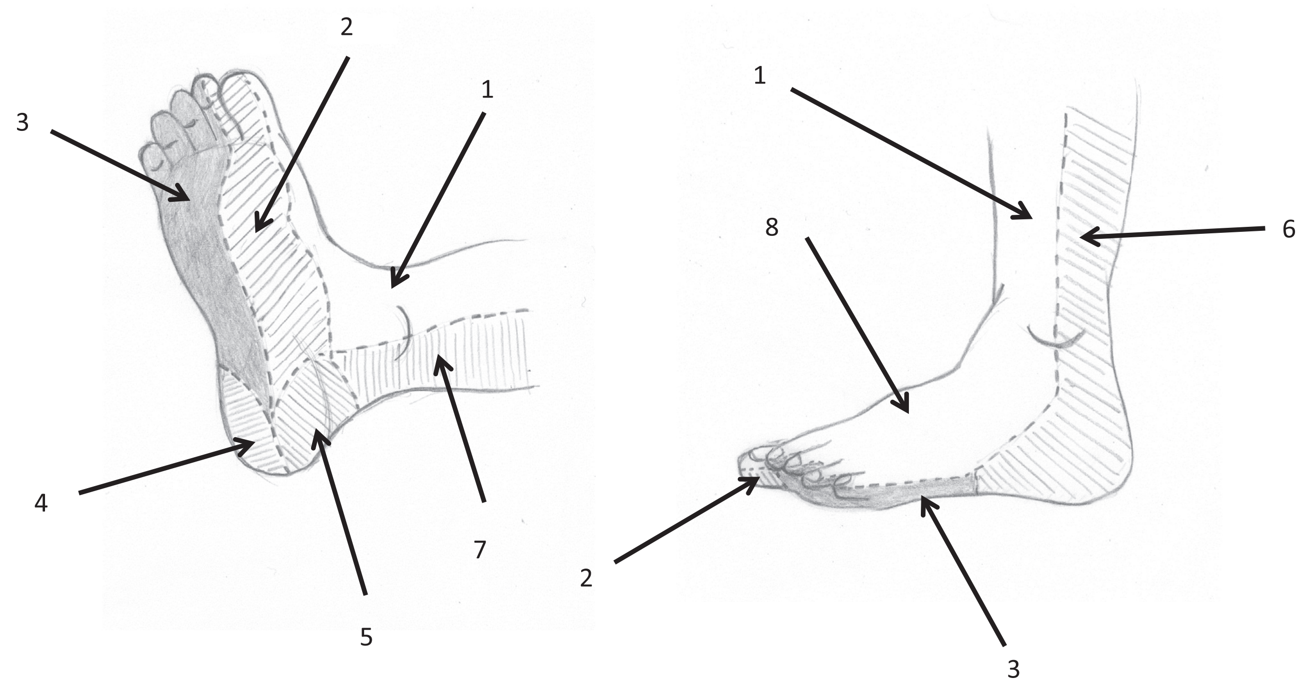

Legends for figure 1

1. Anterior tibial artery
2. Medial plantar artery of posterior tibial artery
3. Lateral plantar artery of posterior tibial artery
4. Lateral calcaneal branch of peroneal artery
5. Medial calcaneal branch of posterior tibial artery
6. Peroneal artery
7. Posterior tibial artery
8. Dorsalis pedis artery of anterior tibial artery

Fig. 1 – Schematic drawings of the foot showing six angiosomes based on anterior tibial, posterior, and peroneal arteries. Adapted from [15].

possible blood supply to the foot. In practice this is not always feasible, and in order to guide the choice of which BTK vessel should be revascularized, the angiosome concept has been proposed, based on the idea that specific anatomical regions are perfused by specific arteriovenous bundles. The concept has been used for planning surgical access, tissue reconstruction, and amputation [5]. This article will discuss the angiosome concept and its application in patients with CLI, and will provide a review of the current literature.

2. The angiosome concept

The angiosome concept has been conceived based on anatomical studies in plastic reconstructive surgery [6]. The term *angiosome* is derived from the Greek *angio-* meaning vessel, and *somite* meaning segment or sector of the body (derived from *soma* meaning body). These studies identified three-dimensional blocks of tissue (consisting of skin, subcutaneous tissue, fascia, muscle, and bone) that are perfused and drained by specific angiosomal vessels.

In the region of the ankle and the foot, there are six angiosomes that emerge from the three main BTK arteries (anterior and posterior tibial artery and the fibular [peroneal] artery) [7]. Primary supply to the skin originates from direct cutaneous arteries, and these are reinforced by small, indirect branches from arteries that supply the deeper lying areas. In healthy subjects, two types of anastomotic arteries create a compensatory pathway between the various angiosomal territories: reduced-caliber ("choke") and similar-caliber ("true") anastomotic arteries that provide a redundant conduit allowing a certain angiosome to receive blood from a neighboring angiosome in case of occlusion of the original source artery [6]. The choke vessels demarcate the border of each angiosome [8].The longer a patient suffers from diabetes, the more these choke vessels will be compromised and the less collateralization can occur. In addition to the choke vessels, direct arterial–arterial connections between angiosomes exist and these connections play an important role in compensating for ischemic events that occur in a neighboring angiosome [8]. As the collateral capacity is negatively affected by occlusive disease of the foot arteries, angiosome-targeted and more distal selective revascularization can be expected to improve outcomes [5,8].

There are six foot angiosomes, including three angiosomes originating from the posterior tibial artery, one angiosome from the anterior tibial artery, and two angiosomes from the peroneal artery [9] (Fig. 1). The following description is based on a paper by Clemens and Attinger [10].

2.1. *Posterior tibial artery angiosomes*

At the level of the foot, the posterior tibial artery gives off the posterior medial malleolar branch at the level of the medial malleolus. The posterior medial malleolar branch joins the anterior medial malleolar branch from the anterior tibial artery, giving rise to an important interconnection between the posterior tibial artery and the anterior tibial artery. This system supplies the medial malleolar area. At the same level, the medial calcaneal artery originates from the posterior tibial artery inferiorly and divides into multiple branches that supply the heel. The angiosome boundary of the medial calcaneal artery includes the medial and plantar heel, with its most distal boundary being the glabrous junction of the lateral posterior and plantar heel. The posterior tibial artery then runs through the calcaneal canal (below the flexor retinaculum) and bifurcates into the medial and lateral plantar arteries. The angiosome boundaries of the medial plantar artery encompass the so-called "instep." The boundaries of this angiosome are posteriorly the distal-medial edge of the plantar heel, on the lateral side the midline of the plantar midfoot; distally the proximal edge of the plantar forefoot; and medially a curved line that runs 2 to 3 cm above the medial glabrous junction. The medial plantar artery has two main branches: the superficial and deep branches. The superficial branch has interconnections with the anterior tibial tree: cutaneous braches connect proximally with medial cutaneous branches from the dorsalis pedis artery and distally with branches of the first dorsal metatarsal artery. More plantarly and laterally, the superficial branch of the medial plantar artery joins with the deep branch of the medial plantar artery and the first plantar metatarsal artery (which is a branch of the lateral plantar artery). The deep branch of the medial plantar artery has perforating branches that supply the medial sole of the foot. At the neck of the first metatarsal, it anastomoses with the first plantar metatarsal artery and/or the distal lateral plantar artery. The angiosome of the lateral plantar artery includes the lateral plantar surface as well as the plantar forefoot. It is bordered posteriorly by the distal lateral edge of the plantar heel, medially by the central raphe of the plantar midfoot, more distally by the glabrous juncture between the medial plantar forefoot and the medial distal dorsal forefoot, and laterally by the glabrous junction between the lateral dorsum of the foot and the plantar surface of the foot. The distal border includes the entire plantar forefoot. The hallux is usually part of the lateral plantar angiosome, but it can also be part of the medial plantar artery angiosome or of the dorsalis pedis angiosome. The lateral plantar artery anastomoses directly with the dorsalis pedis artery distally in the proximal first interspace. This direct anastomosis between the dorsal and plantar circulation helps ensure that if either the proximal dorsalis pedis or lateral plantar artery becomes occluded, flow is maintained to the entire foot. The four plantar metatarsal arteries originate from the deep plantar arch to nourish the plantar forefoot.

2.2. *Anterior tibial artery angiosome*

The anterior tibial artery nourishes the dorsalis pedis angiosome that perfuses the dorsal aspect of the foot and toes as well as the upper anterior peri-malleolar vessels. At the level of the lateral malleolus, the anterior tibial artery gives off the lateral malleolar artery that joins with the anterior perforating branch of the peroneal artery. At the same level, it also gives off the medial malleolar artery, which anastomoses with the posteromedial malleolar branch of the posterior tibial artery. The anterior tibial artery becomes the dorsalis pedis artery once it crosses the extensor retinaculum of the ankle. The angiosome of the dorsalis pedis artery encompasses the entire dorsum of the foot. This artery has connections with the superficial medial plantar artery medially, the calcaneal branch of the peroneal artery proximolaterally, and the lateral plantar artery and its perforators in the proximal metatarsal interspaces. The dorsalis pedis artery is absent or extremely attenuated in 12% of cases, and there are many anatomic variations to its course. Typically, the dorsalis pedis artery has three lateral arterial branches (the proximal and distal tarsal arteries and the arcuate artery) and two medial branches (the medial tarsal arteries). The proximal lateral tarsal artery communicates with the calcaneal branch of the peroneal artery and it may also connect with the lateral malleolar artery and the arcuate artery. The third lateral branch of the dorsalis pedis, the arcuate artery, takes off at the level of the first tarsal–metatarsal joint and travels laterally over the bases of the second, third, and fourth metatarsals. It gives off the second, third, and fourth dorsal metatarsal arteries before it joins the lateral tarsal artery. Medially, the dorsalis pedis artery (usually) gives off two medial tarsal arteries.

2.3. *Peroneal artery angiosomes*

The peroneal artery bifurcates (forming a delta) into the anterior perforating branch and the lateral calcaneal branch emerges at the level of the lateral malleolus, before it emerges at the level of the lateral malleolus. The peroneal artery provides blood supply to the lateral calcaneal angiosome, responsible for the perfusion of the lateral and plantar aspect of the heel and the anterior perforator angiosome (providing a connection of the anterior peroneal perforating branch to the anterior tibial territory; perfusion of the lateral anterior upper ankle). The proximal boundaries of the angiosome of the lateral calcaneal branch extend medially to the medial glabrous junction of the heel, distally to the proximal fifth metatarsal, and superiorly to the lateral malleolus. The lateral calcaneal artery terminates at the level of the fifth metatarsal tuberosity, where it connects with the lateral tarsal artery. The heel has two overlapping source arteries: the medial and lateral calcaneal arteries, ensuring duplicate blood supply to an area that is regularly traumatized during ambulation. Anatomical variants of the above-mentioned anatomy are common, and may occur in up to 16% of cases [11].

3. Application of the angiosome concept in clinical practice

When discussing the angiosome concept, it should be kept in mind that the concept is an anatomic description rather than a physiologic model [12]. Arterial–arterial connections allow for blood flow to the entire foot even when one or more arteries are occluded [10]. Angiosome-oriented revascularization has gained attention and its application has resulted in higher rates of limb salvage and wound healing [1]. However, many factors must be considered in choosing the target artery

Fig. 2 – Photo of forefoot showing ulcer on dorsum of the foot (arrow) and location of pulse of dorsalis pedis artery (arrowhead); note signs of skin and toe ischemia. The location of the ulcer precludes a dorsalis pedis bypass.

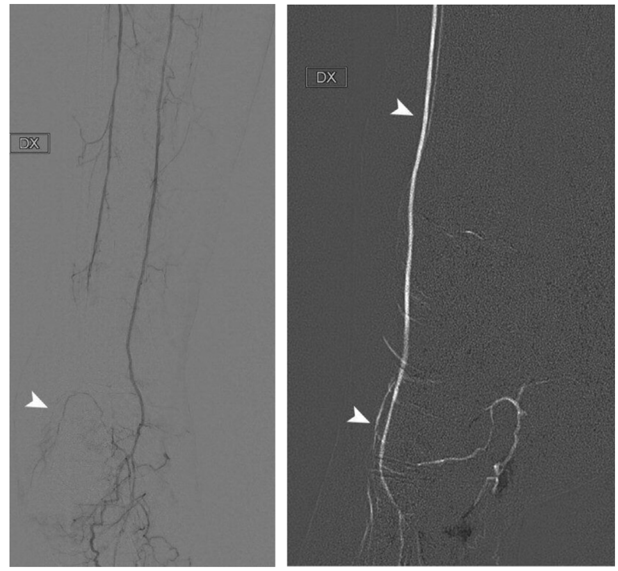

Fig. 3 – Left: angiographic images of foot shown in Figure 1 showing patency of peroneal and posterior tibial artery; occlusion of the anterior tibial artery and faint enhancement of the dorsalis pedis artery (arrowhead). Right: after endovascular treatment antegrade flow in the anterior tibial and dorsalis pedis artery (arrowheads) is demonstrated.

for revascularization, and the angiosome concept should be part of this [13].

It has been suggested that in diabetic patients, the occurrence of (neuro-)ischemic problems (the so-called “diabetic foot”) is related to a combination of distal atherosclerotic macroangiopathy and an impairment of the functionality of the microcirculation (the latter induced by neuropathy and local sepsis) [9,14]. Huge collateral depletion, as seen in diabetic patients and those with end-stage renal disease, jeopardize the natural “rescue system” between the angiosomes [15]. Collateral reserve is depending on aging, the underlying pathology that causes CLI, and the location of the angiosome itself (the two extremes are the atherosclerotic, non-diabetic middle-aged patient with forefoot trophic lesions and, on the other hand, the aged, long-lasting diabetic or renal patient with neuro-ischemic heel tissue defects). In patients with diabetic end-artery disease, so-called “patchy atherosclerosis” occurs, with acute septic thrombosis and loss of small collaterals [5]. The absence of collateral vessels underscores the need for a more distal, selective, revascularization that improves perfusion at the level of the skin [5].

Whereas in surgical revascularization, oftentimes the most suitable vessel for revascularization needs to be chosen (not necessarily the artery that directly supplies the angiosome involved), endovascular revascularization offers the advantage that the specific angiosome can be targeted (although this may require lengthy and cumbersome, not always successful, procedures) [9], and multiple BTK and even below-the-ankle vessel reconstructions can be performed [5]. Bypass still holds an important role because it will yield higher local pressure and physiological pulsatile flow [15]; however, endovascular therapy offers the option to open more than one tibial vessel. Angiosome-guided bypass surgery is not always possible because of the presence of infection, extensive tissue loss (especially when at or near the anastomotic site (Figs. 2 and 3), and severe arterial disease [16]. Both surgical and endovascular procedures may be hampered by the presence of medial sclerosis, with diffuse calcification, that may render the most appropriate (angiosome-related) artery also the most difficult to treat. This problem was limiting endovascular direct revascularization in the past [3], but with the more frequent use of dedicated endovascular material and the more liberal use of retrograde access this technical limitation is probably less of an issue today.

Clinical reports suggest an advantage of direct revascularization, and its importance in diabetic patients is thought to be greater due to the different underlying pathophysiology. In diabetic patients, the tunica media is affected rather than the intima, leading to a situation where not only the source artery but also collaterals and anastomoses between angiosomes are affected [2]. It must be kept in mind that indirect revascularization can be adequate when sufficient collaterals are present (Figs. 4 and 5) [17]. In fact, critics of the angiosome concept suggest that the chronic, progressive nature of peripheral arterial disease leads to the development of collateral arterial connections between the feeding vessels and the wound area [18].

In the diabetic patient, additional factors that influence outcome are peripheral autonomic denervation and regional sepsis, which both cause additional local hemodynamic changes. Endothelial dysfunction results in significant inflammatory changes of the arterial wall and atherosclerosis, and also vascular smooth muscle cells become dysfunctional, which accelerates the process. Microvascular dysfunction also has effects on the autonomic nervous system, with loss of autoregulatory function, an impaired hyperemic and inflammatory response, loss of the neurogenic regulatory response, loss of the vasoconstrictor response, increased arteriovenous shunting, impaired oxygen diffusion, and leukocyte migration. These regulatory functions and responses are essential

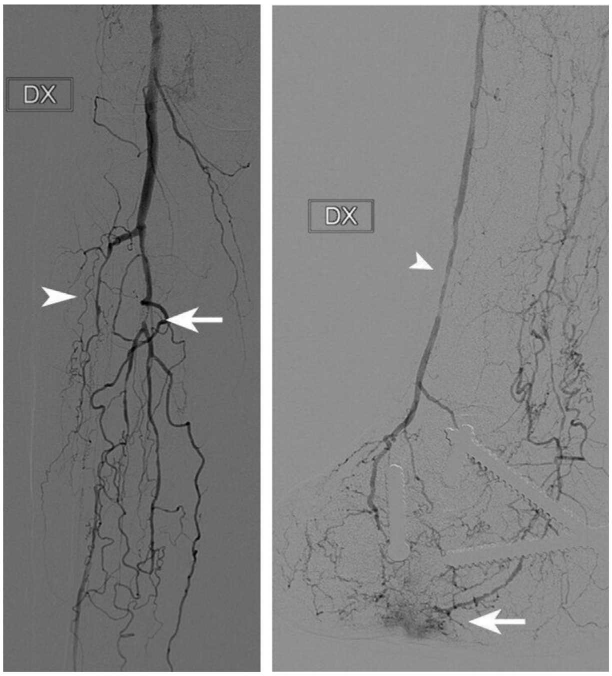

Fig. 4 – Angiographic images of a diabetic patient with a lateral mal perforans ulcer showing occlusion of anterior tibial artery (arrowhead) and tibioperoneal trunk (arrow), absence of distal filling of peroneal and posterior tibial artery.

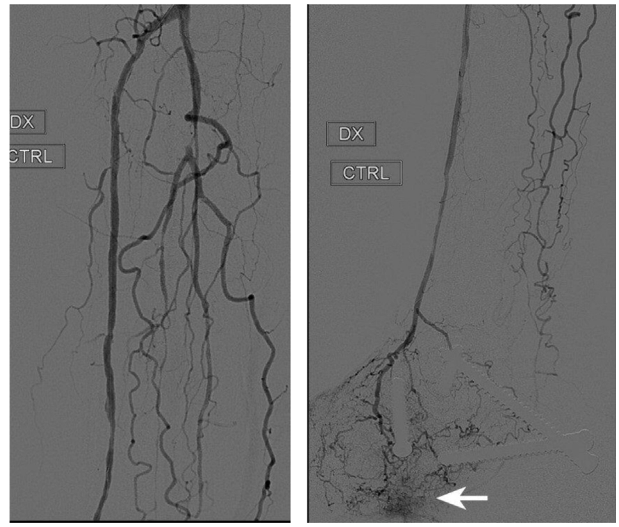

Fig. 5 – Angiographic image after recanalization and balloon angioplasty of the anterior tibial artery showing patency of the proximal anterior tibial artery and a significant increase in wound blush.

for wound healing to progress in an orderly and timely sequence and contribute to faulty wound healing in patients with diabetes. Microvascular dysfunction is not an occlusive phenomenon and supports an aggressive approach to treating existing macrovascular atherosclerotic occlusive disease complicating diabetic wounds of all extremities combined with optimal management of diabetes, wound care, systemic infection, and other known risk factors [14].

The feasibility of angiosome-targeted endovascular revascularization and the number of angiosomes involved was evaluated retrospectively in 161 patients (the majority with diabetes). Only 24% of patients had involvement of a single angiosome (47% has two angiosomes, 26% had three angiosomes, 2% had four angiosomes, and 1% had five angiosomes). Direct flow in the involved angiosome could be achieved in 60.9% of all cases (although it was considered to be feasible in 80.1% of cases, indicating a relatively high failure rate). If the lesion was limited to one angiosome, direct revascularization could be achieved in 69.2% of cases, with extension of the ulcer into two angiosomes this was possible in 86.7% of cases, with three angiosomes involved in 85.7%. When four angiosomes were involved in only one-quarter of the patients, direct revascularization was possible, and in those patients with an involvement of more than five angiosomes, direct revascularization was not possible at all. In the series from Rashid [19], direct revascularization was feasible in only 47% of cases. In the study from Zheng et al [20], 20% of the patients could not undergo angiosome-oriented revascularization due to occlusion with severe calcification or technological difficulties. Because of the frequently present extension of a wound in diabetic patients beyond one angiosome, determining which vessel to target for may be less straightforward than anticipated [21]; classification of wounds proved ambiguous in 23.3%. In the same group of patients, multiple wounds with dispersion over several angiosomes were present in 8.6%.

Perfusion studies using tissue oxygen saturation foot-mapping have shown that there is no perfect correlation with the classical angiosomes [22]. The technique was able to identify areas of ischemia, and can be used to evaluate what the authors have called the “real” angiosome. The angiosome model is not always able to describe the actual distribution of peripheral tissue perfusion because the blood flow depends on additional factors, such as the development of collaterals and vascular abnormalities at the capillary and microvascular plexus level. The “real” angiosome model takes into account both collateral development and anatomical variants. In obtaining tissue healing revascularization alone is not sufficient. Therefore, multidisciplinary care that addresses proper wound care, control of local neuropathy, diabetes regulation, and treatment of local sepsis is mandatory [23].

4. Does angiosome revascularization improve healing?

Several meta-analyses have been published recently on the topic of angiosome-targeted revascularization and, hereafter, an overview of these and single-center series will be given. No randomized trials comparing direct revascularization to indirect revascularization have been performed and, given the complexity of the disease entity, this will probably never be feasible [18]. The validity of the angiosome concept in the treatment of CLI remains controversial, and whether better wound healing and limb preservation is achieved using a direct (angiosome-based) revascularization approach remains a topic of debate. It must be kept in mind that the angiosome concept has been developed in "healthy" subjects, in the absence of peripheral vascular disease, and that direct revascularization is not always possible [24].

4.1. *Single-center studies*

In a study focusing on endovascular treatment in isolated BTK disease, it was found that amputation-free survival and freedom from major adverse limb events out to 4 years was significantly lower in patients that underwent indirect revascularization. It was also found that factors associated with major amputation in the direct group (high hemoglobin A1c level [indicating poor glycemic control] and cilostazol administration) were different from those in the indirect group (high C-reactive protein level, indicating infection) [3]. It was also found that the presence of three BTK runoff vessels at the end of the procedure resulted in the best limb salvage rate in the overall cohort (freedom from major amputation at 3 years overall and according to number of patent runoff of 86% for three *v* 63% for one). Comparing patients with three-vessel runoff and those with direct revascularization (irrespective of the runoff status) showed no significant difference in freedom from amputation.

Evaluation of the endovascular treatment of 250 legs with diabetic foot ulcers comparing direct and indirect revascularization showed significantly better healing rates at 6 and 12 months for the direct revascularization group [4]. After multivariate analysis, direct in-line flow was found to be the only significant independent predictor for ulcer healing. The authors' postulate the reason for improved healing was the loss of "choke" vessels in this diabetic population. The study of Iida et al [25] demonstrated that wound healing is better when performing a direct revascularization as compared to indirect revascularization, while the occurrence of major adverse limb events and amputation rates remained unaffected.

In patients undergoing distal bypass surgery, it was found that the healing rate in the indirect revascularization group was significantly slower than in the direct revascularization group (especially in patients with end-stage renal disease) [16]. Using propensity score analysis, it was found that healing rates were similar. These outcomes are in contrast with a recent study from Spillarova et al [26], who found that end-stage renal disease, diabetes, Rutherford category 6, and low albuminemia were negative predictors of wound healing. This underscores the need for a multidisciplinary approach when correction of metabolic abnormalities when present. When direct versus indirect revascularization was evaluated in patients with combined endovascular and surgical treatment, the highest wound healing rate was achieved after direct surgical bypass to an angiosome artery, and the lowest with indirect angioplasty. In this study, there was a difference in type of lesions/patient treated: balloon angioplasty was performed as first-line treatment in patients with short occlusions and stenotic lesions and to patients with an increased risk of undergoing bypass surgery or without an available autologous vein. This may have introduced a certain bias in the evaluation of the results. In this study, a sub-analysis of collaterals was performed. The presence of collaterals was graded as good or non-existent, and patients were divided into three groups: direct revascularization (in the surgical group in 66.8% of cases, in the endovascular group in 56.5%), indirect revascularization with good collaterals (in the surgical group in 12.2% of cases, in the endovascular group in 30.8%), and indirect revascularization with no collaterals (in the surgical group in 21% of cases, in the endovascular group in 12.7%). The endovascular group underwent more frequently a re-intervention. A univariate analysis demonstrated that C-reactive protein <10 mg/dL, hypercholesterolemia, the type of procedure, and the number of affected angiosomes fewer than three were associated with amputation-free survival. The latter seems to be a logical and foreseeable outcome because the involvement of fewer than three angiosomes indicates the presence of less-extensive disease. This is in line with the findings of the same group at an earlier point in time [27]. On the other hand, increased age, chronic heart failure, chronic kidney disease, hemodialysis, atrial fibrillation, and chronic obstructive pulmonary disease were associated with decreased amputation-free survival. Direct bypass, indirect bypass, and direct percutaneous transluminal angioplasty, as opposed to indirect percutaneous transluminal angioplasty, were independent predictors of amputation-free survival. After surgical bypass, there was no difference between direct and indirect revascularization in wound healing and limb salvage. Leg salvage was similar after direct endovascular revascularization and direct/indirect surgical bypass. Some studies have suggested that the success of wound healing depends on the quality of the pedal arch, but this could not be reproduced in this study (no difference in outcome complete and incomplete arch).

Direct revascularization to pedal angiosomes using bypass with autogenous vein leads to a more efficient wound healing, with the caveat that this type of revascularization is only possible in around 50% of patients [28]. In this study, the location could be assigned to only one single angiosome in only 36% of wounds. Although direct revascularization was shown to improve wound healing, there was no influence on amputation-free survival. Faster wound healing might, however, contribute to better quality of life, as well as to a decrease of costs related to wound care. Pedal arch quality did not influence healing and infrapopliteal bypass outcome in a study that investigated the effect of direct revascularization in the presence of a complete or incomplete pedal arch [19]. Direct revascularization led to significantly shorter healing times in patients without a pedal arch only. Endovascular reconstruction of the pedal arch can probably reduce the time to healing in these patients.

An evaluation of 64 patients with only a single vessel crossing the ankle treated with direct or indirect revascularization (by either surgical or endovascular means) showed a benefit of direct revascularization in terms of wound healing, but failed to demonstrate a difference in limb salvage rate [29]. Comparing the mean time to complete healing in a cohort of 56 patients with 60 wounds, no statistically significant difference was seen between direct and indirect (bypass) revascularization [13]. However, wound healing rates were significantly better in the direct revascularization group (90.9% *v* 61.9% for the indirect revascularization group). In the indirect revascularization group, a significantly higher major amputation rate was seen. In contrast to these findings, Lejay et al [30] (evaluating a small group of 54 patients, 58 limbs with isolated BTK bypasses) found a shorter median ulcer-healing time after direct revascularization, with similar survival and primary patency. Limb salvage rate was also higher in the direct group. In this study, all patients in the indirect group only had one crural artery, which may have influenced outcomes.

A study from France that reported on the outcomes of 157 endovascular procedures (slightly more than half of these procedures were limited to the infrapopliteal segment alone) showed favorable long-term results and failed to demonstrate any impact of the angiosome concept on clinical success [31]. The fact that multi-segment pathology was treated in slightly fewer than half of the patients may have confounded the outcome (for this reason, this study was probably excluded from the most recent meta-analysis described hereafter). The results of an evaluation of 486 patients that were treated by endovascular means where categorization into three groups was performed (direct revascularization, indirect revascularization through collaterals, and indirect revascularization without collaterals) [20], showed that during the 1-year follow-up, the unhealed ulcer rate of the indirect revascularization without collaterals was significantly higher, and the limb salvage rate was significantly lower than in the other two groups. There were no differences in the unhealed ulcer rate or the limb salvage rate between the direct revascularization group and the indirect revascularization through collaterals group. Within the group of indirect revascularization without collaterals, the unhealed ulcer rate of diabetic patients was higher than that of patients without diabetes, but there was no difference in the limb salvage rate between diabetic and nondiabetic patients. No differences in the unhealed ulcer rate or the limb salvage rate were found between diabetic and nondiabetic patients in the other two groups. This study also evaluated the reintervention rate at 1 year and found that there was no statistically significant difference in the percentage of reintervention between direct revascularization and indirect revascularization through collaterals, while indirect revascularization without collaterals led to significantly more reinterventions (compared to the other two strategies). Collateral vessels play a more important role in CLI accompanied by diabetes than in simple atherosclerotic CLI.

Angiosome research has focused on healing comparison of direct versus indirect revascularization. However, in clinical practice, both approaches are used in some patients. This so-called combined revascularization can be achieved in around 10% of cases [32]. Amputation-free survival and the combined re-intervention and amputation-free survival were significantly improved compared to indirect revascularization in this study involving 250 subjects. Wound healing rates were similar, and in diabetics, no differences were seen regarding amputation-free survival and re-intervention rates.

4.2. *Systematic reviews and meta-analysis*

Over the last few years, several systematic reviews have been published and their conclusions are not equivocal, just like the single-center studies described here.

The first systematic review, dating back to September 2013, evaluated 11 studies, involving 1,616 patients and 1,757 limbs [33]. The authors noticed an important heterogeneity of the published data, not only with regard to the technique used, but also the definition of direct revascularization, follow-up, and reporting of outcome. They emphasize the lack of prospective trials; large patient populations; and a consistent, uniform vocabulary to compare study findings. All of these factors prevent (according to the authors) a recommendation of the conceptual model for the guidance of revascularization attempts at a wider level.

The second published review (January 2014) included a total of nine studies (of note, fewer studies were included compared to the review mentioned previously) [8]. A total of 715 legs were treated using a direct approach, while 575 legs were treated with indirect revascularization. The risks of unhealed wound and major amputation were significantly lower after direct revascularization compared with indirect revascularization. Pooled limb salvage rates after direct and indirect revascularization were 86.2% versus 77.8% at 1 year and 84.9% versus 70.1% at 2 years, respectively. The analysis of three studies reporting only on patients with diabetes confirmed the benefit of direct revascularization in terms of limb salvage. Amputation-free survival (evaluated only in two of the included studies) showed a trend in favor of direct revascularization. When feasible, direct revascularization of the foot angiosome affected by ischemic tissue lesions may improve wound healing and limb salvage rates compared with indirect revascularization. A limitation of all of the studies evaluated was their retrospective nature, with a lack of proper comparability of the studies. Not having data on the angiographic status of the foot arteries limits the analysis of the data further and most data involve diabetic patients, making it uncertain whether angiosome-targeted revascularization is also of benefit in non-diabetic patients. Therefore, additional studies of better quality and adjusted for differences between the study groups are needed. An invited commentary to this review underscores the fact that the angiosome model was developed in healthy subjects and that the actual distribution of angiosomes may be different in patients with CLI [24].

The third review, published in May 2014, included 15 cohort studies (that reported on 1,868 limbs), including both endovascular and surgical revascularization [17]. The quality of evidence was low or very low for all outcomes evaluated. All studies were retrospective and observational in nature. None of the included papers used a standardized revascularization decision-making algorithm. Compared to indirect (not angiosome-related) revascularization, patients that underwent direct revascularization were significantly more likely to be revascularized to the anterior tibial and dorsalis pedis artery and significantly less likely to the peroneal artery (this may be a confounding factor). Direct revascularization was associated with improved wound healing rates compared with indirect revascularization, and also demonstrated significantly improved limb salvage rates. Wound healing and limb salvage were improved for both open and endovascular intervention. There was no effect on mortality or the incidence of reintervention between the two methods of revascularization. The improved outcomes seen when performing direct revascularization can probably be explained by the absence of adequate collaterals between the angiosomes. In cases where good collaterals are present, indirect and direct revascularization lead to comparable outcomes. This underscores the necessity to more aggressively target for direct revascularization in the absence of collaterals. In addition, as mentioned, combining indirect and direct revascularization has been demonstrated to lead to better outcomes [34]. This meta-analysis suggests that in patients where both options of the direct and indirect approach are feasible, direct revascularization should be the preferred approach.

The fourth meta-analysis selected only 4 of 518 publications [35]. The largest number of papers was excluded because they were duplicate publications or papers from an institution describing an increasing number of patients in prospectively recruited cohorts in various papers. This review was also limited to diabetic patients treated by endovascular means. It was found that both the overall limb salvage rate and wound healing were significantly better after angiosome-targeted angioplasty.

The most recent systematic review and meta-analysis enrolled studies including open and endovascular revascularization, as well as diabetic and non-diabetic patients with CLI [36]. A total of 19 cohort studies (with 3,932 patients) were evaluated. Nine of these were considered as high quality. It was found that direct revascularization led to significantly better wound healing. Direct revascularization in bypass studies did not show a reduction of major amputations compared to indirect revascularization. A significant reduction of major amputations was seen in high-quality studies, and those studies evaluating endovascular treatment. Survival rates were similar. In 3 of 19 studies, a stratification was made for collaterals. In the presence of collaterals, no differences in wound healing and major amputation rate were seen between angiosome-targeted and non-angiosome–targeted revascularization.

5. Conclusions

Predicting diabetic foot healing based on angiosome perfusion remains a matter of debate, and only a randomized trial will be able to answer this clinical question definitively. Current studies (including the systematic reviews) show inconsistent methodology; heterogeneity; lack of definition; and (especially in the earlier reviews) a different number of studies included, although the same number was probably available for evaluation. The focus of the angiosome concept has been on revascularization, but it should be kept in mind that there is also a significant role in determining safe incisions in normal and vascular compromised patients [10]. Today there is a better understanding of the role of the "choke" vessels in diabetic and renal patients, the importance of the foot arches and large arterial–arterial collaterals, and the key role of metatarsal perforators [37]. Distinctions should be made between direct, indirect via arterial–arterial connections, and "pure" indirect revascularization. In the latter, healing will depend on whether choke vessels eventually open up or not [38]. The importance of direct revascularization depends on the way the arterial outflow is preserved, and even indirect revascularization through collaterals may provide results similar to those of direct revascularization. Probably the greatest value of angiosome-based revascularization is for patients in which the lesion is limited to a single angiosome, or in cases where healing of postsurgical amputation wounds is needed (in these cases, the connection between the dorsal and plantar circulation has been interrupted). The concept may be less relevant for endovascular revascularizations because, in contrast to bypass surgery, it offers the option to reopen multiple vessels [4]. In the various studies presented, the patients who undergo angiosome-targeted revascularization as opposed to non-targeted revascularization are different with regard to age, comorbidities, and severity of peripheral arterial disease. Oftentimes patients are too fragile for open surgery, and thus the only option is endovascular revascularization. Furthermore, in a large proportion of patients, the target vessel for revascularization cannot be chosen, as there may be only one crural vessel left, while the wound affects several angiosomal regions. Therefore, in the minority of cases, it is possible to choose between angiosome-targeted and non-angiosome–targeted revascularization or between percutaneous transluminal angioplasty and open bypass. It is therefore beneficial to be able to offer both methods of revascularization. Whenever there is a possibility to achieve angiosome-targeted revascularization, endovascular treatment is the best option. If not, however, the best option seems to be bypass surgery, regardless of the angiosomal orientation [27]. When choosing between surgical and endovascular revascularization, the completely different levels of invasiveness of the procedures must also be kept in mind. In view of the inflow interruption to the periphery and blood loss as a result of open surgery, endovascular procedures are not just less invasive to the patient, but they also have a lower risk of postoperative infection, as well as shorter hospitalization time.

Challenges for proper implementation of the angiosome concept are twofold. First, a change of mindset should occur, letting perfusion of an affected area prevail over the reconstitution of perfusion of the most suitable artery. Second, anatomical variations of the main angiosome boundaries occur occasionally [5]. When using the angiosome concept, the definition of angiosome-targeted (direct) revascularization is of critical importance. In the literature, two definitions of direct revascularization in patients with a foot ulcer spreading over the forefoot and heel are used, and when different definitions are used, different outcomes may be seen [39]. In definition A, direct revascularization is considered to be performed if any of the affected angiosomes are revascularized (eg, a lesion of the tip of the toes can either be revascularized through the anterior tibial/dorsalis pedis artery or posterior tibial/plantar artery). Definition B accepts one angiosome revascularization only (in the case of a forefoot lesion only the posterior tibial/plantar artery should be considered). In this specific study, the use of definition B yielded a direct revascularization rate of only 30%, and when using definition A, the rate went up to 56%. When looking specifically at the impact of the two different definitions, it was noted that definition A of direct revascularization was associated with significantly better wound healing and lower amputation rates, whereas definition B was associated with significantly better wound healing only. It can therefore be concluded that if the wound spreads out over more than one angiosome (in the forefoot or heel), any angiosomal artery can be targeted in order to achieve a better outcome. This is a very important finding because the majority of studies does not report the number of affected angiosomes, or provides insight in the definition used.

Important factors that should be considered when planning the treatment are the number of affected angiosomes and C-reactive protein level [27]. Five factors inhibit wound healing after revascularization [16]:

1. location and extent of ischemic tissue defects
2. systemic factors relating to wound healing ability and the defense system
3. infection
4. inadequate topical treatment
5. insufficient blood supply due to inadequate revascularization

In all cases, delay of treatment should be avoided: longer standing infection and the related elevation of C-reactive protein are known factors that influence outcomes negatively. The threshold for intervention in diabetic patients with a foot ulcer should be lower than that for non-diabetic patients [4]. If technically feasible, direct revascularization is probably the best way to achieve appropriate wound healing because it will provide optimal macro- and microcirculatory conditions for tissue regeneration. This is especially the case in patients with end-stage renal disease and diabetic patients in whom collateral circulation is often compromised. Reconstitution of macrocirculation should also focus on re-opening of foot arches and large collaterals. Achieving pulsatile arterial flow straight to the site of the ischemic wound is of critical importance to effectively treat wound infection, to accelerate the healing process, and to avoid limb loss [8].

As mentioned previously, in all studies outcomes have not been well defined, and there may be a need for more objective evaluation of the hemodynamic changes by using skin perfusion pressure measurement, hyperspectral imaging, indocyanine green staining, or two- or three-dimensional perfusion angiography [16,33]. Recent research measuring microperfusion using light-guided Doppler flowmetry demonstrated that there was global improvement in tissue perfusion of the foot immediately after tibial angioplasty. This effect was not restricted to certain borders, such as the ones defined by the angiosome concept [40]. Although this study involved relatively small numbers and design flaws, the findings provide food for thought about the presumption that angiosome-based revascularization is crucial [41]. Achieving the goal of optimal revascularization is more complicated than it appears at first sight and collateral flow developed as a response to chronic ischemia may lead to better trans-angiosomal flow than would be anticipated. This fits with the clinical observation that bypass to one part of the foot may successfully treat tissue loss in another [41]. Not all studies evaluating the angiosome concept came to the conclusion that angiosome-directed revascularization is essential. The evaluation of functional anatomy by means of intra-procedural real-time analysis of foot perfusion may offer better guidance to revascularization in the future [18].

Questions for the future remain how (using which type of macro- and microcirculatory evaluation) and when (which phase of reperfusion) direct revascularization will provide consistent tissue regeneration to prove superiority over indirect revascularization [37]. It will never be a matter of debate that restoring pulsatile arterial flow to an ischemic block of tissue promotes healing. Despite all of the recent research, it remains unclear to what extent the angiosome model influences the choice of the revascularization strategy and decision making and how this improves clinical outcomes. It is without doubt that the angiosome model is able to steer decision making, especially in conditions where one needs to target one single artery (eg, in bypass surgery or in an attempt to limit contrast load in patients with end-stage kidney failure). With the endovascular-first approach that is advocated today for diabetic foot treatment, it is possible to perform sequential revascularization of all arteries. This implies that the choice of which artery to target first becomes less stringent and therefore the angiosome model will be of less importance. Furthermore, given the variations in anatomy and the variable amount of collateral reserve, the predefined anatomical, topographical angiosomes do not always correspond to the actual distribution of flow. This underscores the need for proper pre- or peroperative angiographic assessment in order to reliably confirm which artery should be considered as the feeding artery of a wound bed. The old angiosome theory is here to stay, but should be part of a more holistic approach that emphasizes functional revascularization of the diabetic foot.

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