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The Role of The Angiosome Model in Treatment of Critical Limb Ischemia

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1. Introduction

Critical limb ischemia (CLI) is the major cause of amputation in the developed world but revascularization offers an opportunity for limb salvage. Revascularization can be performed either by bypass surgery or by endovascular techniques. Peripheral bypass surgery can be performed using artificial grafts, but vein grafts offer better limb salvage and graft patency [1].

When performing revascularization of the lower limb, common clinical practice and recent guidelines include grafting of the" best vessel" which crosses the level of the ankle in order to restore pulsatile flow to the foot [1]. This may lead to either direct perfusion of the ischemic area or – very often – indirect perfusion relying on collaterals surrounding the diseased zone. This strategy is different from the one used e.g. in coronary artery bypass surgery, where the aim is "complete revascularization" i.e. performing bypasses to every diseased vascular territory [2].

The arterial connections between different parts of the foot may quite often not be sufficient to ensure healing and to prevent amputation. For instance, approximately 15% of heel ulcers do not heal despite an open bypass graft to the dorsal pedal artery [3]

An alternative strategy, called the angiosome model, is based on the pioneering work of Taylor and coworkers [4], who, in the eighties, performed detailed dissections with injection of dye in the vessels. They demonstrated the fact that the body consists of "angiosomes" i.e. three-dimensional blocks of tissue perfused and drained by specific arterial and venous bundles. In a later report from the same group, the angiosomes of the leg and foot were described in detail [5]



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Perfusion and drainage can occur between angiosomes by means of connecting "choke" vessels, but this perfusion is less effective than direct supply from the specific feed artery of the angiosome. It is worth noting that the choke vessels are diseased in patients with diabetes and atherosclerosis. This angiosome has had profound impact on the developement of strategies for plastic and reconstructive surgery. However, only little attention has been paid to the angiosome model in treatment of critical limb ischemia. According to the angiosome model, the specific feed artery – rather than the "best vessel" – should be favoured for revascularization. The foot and ankle area consist of six angiosomes.

During the last few years, some studies have compared the results of "best vessel" versus "angiosome" directed revascularization. The studies include comparisons of both arterial bypass and percutaneous revascularization based on the two principles

This chapter aims at describing the role of the angiosome model in critical limb ischemia, and to review the current literature.

2. Anatomy

Blood supply to the foot is derived from the three tibial vessels, the Anterior tibial artery, the Posterior tibial artery, and the Peroneal artery. These three arteries give rise to six endarteries, each supplying an angiosome (Figure 1).

1. The anterior tibial artery supplies the anterior ankle and continues as the dorsalis pedis artery, which supplies the dorsum of the foot. It gives off the lateral tarsal artery and branches into the first dorsal interosseal artery and the arcuate artery supplying the 2-4 interosseal arteries. It has been pointed out that the dorsalis pedis artery is extremely attenuated or absent in 12% of cases [6].

The posterior tibial artery divides into three main branches:

- **2.** The calcaneal branch, which arborizes into multiple braches, that supply the medial and plantar portion of the heel,
- **3.** the medial plantar artery, supplying the medial, plantar part of the foot. Its boundaries encompass the instep, and, depending on anatomic variability, can include the hallux.
- **4.** the lateral plantar artery which supplies the lateral midfoot as well as the entire plantar forefoot through the 4 plantar metatarsal arteries that emanate from the deep plantar arch. Normally, this angiosome also includes the plantar aspect of the hallux, depending on anatomic variability.

The peroneal artery bifurcates into

- 5. the anterior perforating brach, supplying the lateral anterior upper ankle and
- **6.** a calcaneal branch, supplying the lateral and plantar heel. Together with the calcaneal brach of the posterior tibila artery this artery ensures a double blood supply to the plantar aspect of the heel.

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1. Dorsalis pedis angiosome

- 2. Medial calcaneal artery angiosome
- 3. Medial plantar artery angiosome
- 4. The hallux, which may be supplied by the feeding arteries of angiosomes 1, 2, or 6
- 5. Anterior perforating branch angiosome
- 6. Lateral calcaneal branch angiosome
- 7. Lateral plantar artery angiosome

Figure 1. Angiosomes shown on the surface of the foot. A. Medial view, B. Dorso-lateral view, C. Plantar view.

3. Interconnections

A number of interconnections exist between the angiosomes. When present, these interconnections exist *a priori* and – in contrast to the choke vessels described below - do not need a period of ischemia to open. However, as peripheral arterial disease progresses, these connections may be blocked.

The arterial-arterial connections include:

Anterior tibial to peroneal:

The lateral malleolar artery joins with the anterior perforating branch of the peroneal artery just above the ankle joint (Figure 2A).

Anterior tibial to posterior tibial:

The lateral plantar artery forms the deep plantar arch crossing the proximal 2,3, and 4th metatarsals and finally anastomoses directly with the dorsalis pedis artery in the first interspace (Figures 2A and 2B). The superficial and deep medial plantar arteries join at the cruciate anastomosis. Depending on what arteries predominate at or around the cruciate anastomosis, the hallux may be primarily nourished by the lateral plantar artery, medial plantar artery, the first dorsal metatarsal artery or simultaneously by either two or three of these arteries [7].

The medial plantar artery also interconnects with the anterior tibial tree as cutaneous branches connect proximally with medial branches of the dorsalis pedis artery and distally with branches of the first dorsal metatarsal artery.

Peroneal and posterior tibial connections:

Between one and three communicating branches between the peroneal artery and the posterior tibial artery proximal to the ankle joint deep to the Achilles tendon.

On the other hand, no direct arterial-arterial connection exists between the medial and lateral calcaneal arteries, which both supply the plantar aspect of the heel.

4. Choke vessels

Where no "true" arterial-arterial connections are present between neighbouring angiosomes, a network of reduced caliber "choke vessels" form a link. These vessels are normally inadequate to perfuse the area of a distant angiosome but may be provoked to dilate.

This is the theoretical base of the "delay phenomenon" which has been applied in plastic surgery. While the choke vessels between angiosomes in a skin or muscle flap may be sufficient to perfuse an adjacent vascular territory, necrosis will ususally appear in the choke vessel zone defining the next vascular territory. When designing a skin or muscle flap larger than two angiosomes, a two stage procedure might be performed. In the first stage, the perforators of the neighbouring angiosomes are ligated, causing the choke vessels between neighbouring angiosomes to dilate over a period of 4-10 days. After this delay period, a larger flap can be safely elevated [8]. There is good clinical and experimental evidence that this

principle works for the transfer of skin grafts from essentially normal donor sites. These results may, however, not be extrapolated to other situations e.g. in the ischemic foot where distal, aggressive macroangiopathy is associated with microcirculatory changes like thrombosis, neuropathy, local sepsis, arterio-venous shunting and hypercoagulability [9].



Figure 2. A. Lateral oblique projection of the anterior pedal vessels of a patient with peripheral occlusive arterial disease and patent arterial-arterial connections. ALMB-APB: Connection between the anterior lateral malleolar branch of the anterior tibial artery and the anterior perforating branch of the peroneal artery. DPA-LPA: Perforating branch connecting the dorsal pedal artery with the lateral plantar artery. B. Antero-posterior projection of the perforating branch connecting the dorsal pedal artery with the lateral plantar artery (DPA-LPA).

5. Imaging and assessment

5.1. Angiography

A fundamental prerequisite of providing angiosome-directed revascularization is profound knowledge of the anatomy of the pedal vasculature as well as adequate imaging technique including intraprocedural angiography of both tibial and pedal arteries. Manzi and coworkers have recently reported their experience from more than 2500 antegrade interventional procedures in patients with critical limb ischemia and diabetes [10]. For imaging of the pedal arteries they stress that prolonged filming is often necessary to record delayed enhancement of of pedal vessels from retrograde or collateral circulation and that both standard anteroposterior and lateral oblique projections should be obtained. They have established the following two criteria for correct positioning of the image intensifier: 1) The base of the fifth metatarsal bone must be seen to project outward from the base of the foot in the lateral oblique view and 2) the first proximal metatarsal interspace must be clearly visualized in the anteroposterior view. These two views tend to give a good overview of the pedal arteries and collaterals.

5.2. Doppler ultrasound

Attinger and coworkers have described in detail how to map the arterial-arterial connections using a Doppler device [7].

As an example, the Doppler signal is located from the posterior tibial artery over the tarsal tunnel. If the signal persists when occluding (by digital compression) the artery distally, there is antegrade flow along the posterior tibila artery. If the signal disappears, the flow is retrograde from the anterior tibial artery via the dorsalis pedis and lateral plantar arteries. Similarly, Doppler signal can be obtained from the anterior perforating branch of the peroneal artery in the lateral soft area between the tibia and fibula just above the ankle joint. When the anterior tibial artery is occluded at the takeoff of the lateral malleolar branch, the Doppler signal will persist if there is antegrade flow along the anterior perforating branch of the peroneal artery. If the Doppler signal disappears, filling of the anterior perforating branch must be retrograde from the anterior tibial artery through the lateral malleolar branch. The authors describe how the competence of these connections can have profound significance for the healing potential of an amputation wound.

5.3. Thermography

Nagase and coworkers [11] reported the results of plantar thermography of skin temperature in 129 non-ulcer diabetic patients and 32 normal volunteers. From the pattern of four different plantar angiosomes originally described by Attinger [7], they defined twenty different patterns of temperature distribution. The most common pattern in normal subjects was a "bilateral butterfly pattern" in which the medial arch showed the highest temperature (46.9%) or an even distribution of temperature across the entire planta of the feet (20.3%). Recordings of the diabetic feet showed a lower proportion of feet with a "bilateral butterfly pattern" (13.9%), higher proportions of even distribution of temperature (39.1%) and a generally more diverse distribution of patterns in the rest. Although interesting, the study did not provide comparisons with angiographic findings that could confirm a correlation between the distribution of skin temperature and the distribution of lesions of feed arteries to the relevant angiosomes.

6. Results from direct versus indirect revascularization

A number of studies have been performed comparing the results of direct revascularization to the relevant angiosome with those of indirect revascularization either through collaterals or choke vessels.

In 2009, Neville and coworkers published a retrospective analysis of 43 patients undergoing bypass surgery for tissue loss due to ischemia [12]. Twenty-two were directly revascularized to the relevant agniosome while 21 were indirectly revascularized. Healing occurred in 91% of the directly revascularized patients and only 62% of the indirectly revascularized patients (p=0.03]. Major patient characteristics such as diabetes, tobacco use, and renal failure were evenly distributed between the directly revascularized and indirectly revascularized groups, but wound characteristics and infection were not reported.

On the other hand, Azuma and coworkers [13] reviewed the results of 249 consecutive distal bypasses for critical limb ischemia. 218 limbs were included in the initial analysis which proved significantly lower wound healing rate in the indirect revascularization group than in the direct revascularization group. This was especially the case in a subgroup of patients with end stage renal failure. This finding was, however, compromised by significant baseline differences between the groups especially characterized by a higher proportion of patients with heel ulcers and gangraene in the indirect revascularization group. After applying propensity scored analysis including only 48 pairs of limbs, the healing rate between the two groups did not reach statistical significance (p=0.185). The authors concluded that the angiosome concept was not relevant for open surgical treatment of critical limb ischemia in patients without end stage renal failure. This conclusion may be questioned in view of the limited statistical strength of the propensity scored analysis.

Iida and coworkers reviewed the results of endovascular treatment of 203 limbs in 177 consecutive patients with critical limb ischemia, Rutherford 5 or 6 [14]. During up to 4 years follow up, they found significantly higher limb salvage rate in patients with the directly revascularized than indirectly revascularized wounds. Interestingly, the total number of tibial vessels with run off did not influence the limb salvage rate in neither group, indicating that it is not important how much blood can be provided to the foot but rather whether i t reaches the ischemic area. In a later review by the same group [15], including 369 limbs from 329 consecutive patients, including only patients with isolated below-the-knee lesions, patients who had received direct revascularization experienced significantly higher levels of amputation-free survival and freedom from major adverse limb events than patients in whom only indirect revascularization was possible. In this review the finding was confirmed after propensity matching of groups. In multivariate analysis, elevated levels of c-reactive protein were found to be independent predictors of major amputation in the indirect revascularization group but not in the direct revascularization group. This may imply that indirect revascularization may be inadequate for the healing of infected wounds.

Alexandriescu and collegues have published several reports describing their experience with targeted primary angioplasty of diabetic foot lesions [16-17]. In a series of 124 limbs (98 patients), they were able to achieve direct revascularization in 82% [16]. Limb salvage was 91% at 12 months and 84% at three years follow-up. More recently, they published a historical comparison between their results before and after 2005 when they introduced the angio-some concept in their practice. Despite similar graft patency and technical success, they experienced a significantly better wound healing rate and limb preservation in the group of patients treated according to the angiosome concept [18]. This result is interesting although it is probably biased by the general learning curve of the group.

In a paper published together with Alexandriescu, the vascular surgery department at the University Hospital in Helsinki, Finland recently reported their results from the last three years [19]. In a population including approximately the same number of direct and indirect endovascular revascularizations, they found 74% of the wounds to have healed within one year in the directly revascularized group compared to 46% in the indirectly revascularized group (p=0.002). The number of patients was, however, not reported.

Two studies, one surgical by Deguchi [20] and one endovascular by Blanes Ortí [21] failed to show any difference in wound healing time or limb salvage between directly or indirectly revascularized patients. Due to small numbers, the statistical strengh of these comparisons is, however, limited.

6.1. The influence of collaterals

The prognostic significance of indirect revascularization via collaterals was studied by Varela in a mixed cohort of venous bypass and endovascular treated patients with ischemic wounds [22]. Defining collaterals visible on perioperative angiograms, either between distal calcaneal peroneal branches and anterior or posterior tibial artery (n=16) or patent pedal arch connecting dorsal and plantar blood supply (n=2), they found a similar wound healing rate for indirect revascularization of the wound area through collaterals as for direct revascularization to the angiosome specific feed artery (92% versus 88% wound healing at 12 months follow-up). When including indirect revascularizations without visible collaterals, only 73% of the wounds had healed after 12 months (p=0.008).

6.2. The significance of venosomes

Anatomically, the venous drainage follows the arterial perfusion of the angiosomes [23] and Alexandriescu used the term venosome, when reporting the results of surgical deep calf vein arterialization. In a series of 26 limbs in 25 diabetic patients with very advanced below the knee occlusive disease, a PTFE bypass was made between an arterial inflow and a deep calf vein followed by selective embolization of collaterals, directing arterial blood to the relevant venosome. Using this strategy, a 73% three year limb salvage rate was achieved [24].

7. Discussion

The concept of angiosome-directed revascularization is, theoretically, attractive and in accordance with pathophysiological knowledge. It is also in line with experience from coronary bypass surgery, where reperfusion through collaterals does not provide a similar freedom from cardiac events as that provided by complete direct revascularization of all the diseased vascular territoria [2].

It is well established that healing of an ishemic pedal wound is more effectively achieved when pulsatile arterial blood flow is established across the ankle and it seems logical to expect that this effect is larger when the pulsatile flow is provided all the way to the site of the injury.

As suggested by the above mentioned papers, the effect of direct revascularization may especially be relevant in the settings of end stage renal failure, infected wounds, endovascular rather than surgical repair, and in cases where collaterals are absent.

The angiosome concept represents a novel approach to improving the therapy of critical limb ischemia. It may potentially provide the rationale not only for the choice of target artery. It may also influence the indications for endovascular or open repair according to which target artery is accessible by which method.

Although the evidence in favour of an angiosome directed treatment is mounting fast, it is, however, still circumstantial. All of the studies comparing the results of direct and indirect revascularization are retrospective and, thus, biased by heterogeneity in patient selection. More often than not, the angiosome specific artery will also be the most diseased artery and the ability to recanalize this vessel will most probably select the least atherosclerotic patients to the "direct revascularization" group. It is also likely that the advocates of an angiosome-directed revascularization strategy would attempt direct revascularization first and only perform indirect revascularization if this attempt was unsuccessful. Regardless of any retrospective matching of the groups this would lead to patients with extensive distal atherosclerosis to be placed in the indirect revascularization groups, thus biasing the comparisons in favour of the angiosome specific approach. The differences in healing rate and limb salvage between groups may, therefore, merely reflect preoperative differences in the extent of occlusive disease. It is possible that this is what is reflected in the lack of statistically significant differences after propensity scoring in the study by Azuma [13].

As highlighted in the study by Varela, the presence or absence of collaterals merit further investigation [22]. For this purpose, the Doppler method described by Attinger [7] seems to be a good and non-invasive technique.

As evidence stands at the moment, there is some, although limited, evidence that when there is a choice of target artery for revascularization, preference should be given to the artery directly feeding the wound's angiosome. Specific analysis, based on prospectively collected data of homogeneous cohorts of patients are needed. Unbiased evidence will only be achievable by performing a prospective, randomized controlled trial with a blinded endpoint assessment.



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