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EDUTORIAL

Angiosome Specific Revascularisation: Does the Evidence Support It?

Angiosome specific revascularisation, does the evidence support it? The answer is actually yes and no, depending on the arteries available and whether you accept the findings of the literature as it stands. The evidence to support clinical decision making does exist, but the highest quality papers are meta-analyses limited by the fact that they can only include low quality cohort studies.[1,2] Because of this, the strength of recommendations that can be made is low, and the results are based on procedures involving logical selection bias.

This educational review aims to discuss the main issues around clinical decision making for angiosome directed revascularisation via a clinical vignette, which would be seen commonly in clinical practice (see Box. 1).

Box 1 Key questions

- What is angiosomal revascularisation?
- What literature is available to support decision making when performing endovascular or open tibial artery revascularisation?
- What arteries should actually be targeted during clinical practice to get the best outcomes for the patient?

ANGIOSOMES

The angiosome concept was first described in 1987, defining an angiosome as an area of tissue comprising skin, subcutaneous tissue, fascia, muscle and bone supplied by a specific artery and drained by a specific vein (Fig. 1).[3] It was initially defined by plastic surgeons, so the anatomical assumptions were based on healthy vessels, rather than those diseased enough to require intervention.[4]

In the most common angiosome model the foot consists of six angiosomes: three arising from the posterior tibial artery, two from the peroneal artery, and one from the anterior tibial artery (Fig. 1). Patients with critical limb ischaemia who develop tissue loss in a specific angiosome(s) and undergo tibial artery revascularisation are considered to have a "direct reperfusion" when the artery of interest supplies the area of tissue loss, and "indirect reperfusion" when it does not. This is most commonly defined in the literature using the Taylor and Palmer model.[4] As an example, the most common form of direct reperfusion for tissue loss in the tips of the toes would be via the anterior tibial artery, with indirect reperfusion via the peroneal artery.

Several other angiosome models have been suggested, and, importantly, the changes in the foot vessels in peripheral vascular disease, especially diabetes, may alter this strict angiosomal perfusion pathway. This may confuse direct reperfusion between the anterior and posterior tibial arteries, or lead to a theoretically direct reperfusion (from the normal anatomical model described by plastic surgeons), such as an anterior tibial angioplasty, not actually reperfusing the area of interest because there are no distal vessels supplying the tissue loss.[5]

CLINICAL SCENARIO

A 58 year old man presented with tissue loss to the tips of the first and second toes of the left foot (see Fig. 2 [patient consent provided]). He was a smoker, and was diagnosed diabetic when he presented acutely 4 months earlier with severe foot sepsis of the right foot and leg. When he presented, he was on aspirin 75 mg but no lipid lowering therapy. Atorvastatin 40 mg was added on presentation to hospital. Despite treatment the right leg was amputated owing to a combination of non-reconstructable disease and extensive tissue loss. The left foot was asymptomatic at that time, with a plan for diabetic foot clinic follow up. He did not attend these appointments until he was forced to by the artificial limb centre because of new tissue loss in his left foot. At that point he had palpable femoral and popliteal pulses, with incompressible calf vessels, a toe brachial index (TBI) of 0.3, and an absolute toe pressure of 38 mmHg. Sensation was lost below the level of the ankle.

Computed tomography angiography (CTA) showed essentially normal arteries to the knee with severe tibial disease and no obvious target artery in the foot. After multidisciplinary team discussion he underwent tibial angioplasty. A 4 Fr sheath was inserted into the common femoral artery under ultrasound guidance. Digital subtraction angiography from this showed good flow to the trifurcation with three vessel tibial disease. The anterior tibial artery appeared to be occluded near its origin, as was the posterior tibial. The peroneal artery was stenosed at origin but appeared the best vessel. Because both CTA and digital subtraction angiography from a common femoral sheath can miss target vessels in the foot, selective angiography through a 4 Fr catheter was performed from the popliteal trifurcation (see Fig. 3). Delayed phase imaging showed that the anterior tibial artery was patent to the mid-calf but occluded distally with reconstitution of the dorsalis pedis in the foot. The plantar arch was heavily diseased and probably occluded.

The operator chose to try and reconstitute the anterior tibial artery as this would provide direct reperfusion of the angiosome affected. Re-entry at the dorsalis pedis failed (Fig. 4). The peroneal artery was therefore treated successfully (Fig. 5).

The post-procedural TBI was 0.45, with an absolute pressure of 63 mmHg. The increase in perfusion pressure was sustained and medical therapy optimised. He was treated in a total contact cast.

Figure 1. The most common angiosome model of the leg and foot. Reproduced from Iida *et al*.[3]

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Figure 2. Pattern of tissue loss.

The wounds would not fully heal after several months, despite a sustained increase in TBI. He continued to miss outpatient appointments and ultimately re-presented with severe infected tissue loss requiring major amputation.

In this case, direct reperfusion of the toes via the dorsalis pedis angiosome was attempted but failed; therefore, indirect reperfusion was achieved via the peroneal artery. Are the clinical results what we would expect based on the literature?

THE EVIDENCE FOR ANGIOSOME SPECIFIC REVASCULARISATION

As already mentioned, the literature is very low quality. In terms of comparing direct and indirect revascularisation outcomes, meta-analysis offers the best way to summarise findings.[1,6] There are no randomised trials, and the cohort studies available for meta-analysis have a median Newcastle Ottawa Score (a marker of study quality scored from 0 to 9) of 5, so are of moderate quality. GRADE analysis (which gives the strength of recommendation for an individual outcome from meta-analysis) is low or very low for all outcomes, meaning there is only a low quality or low certainty to the results discussed.[6]

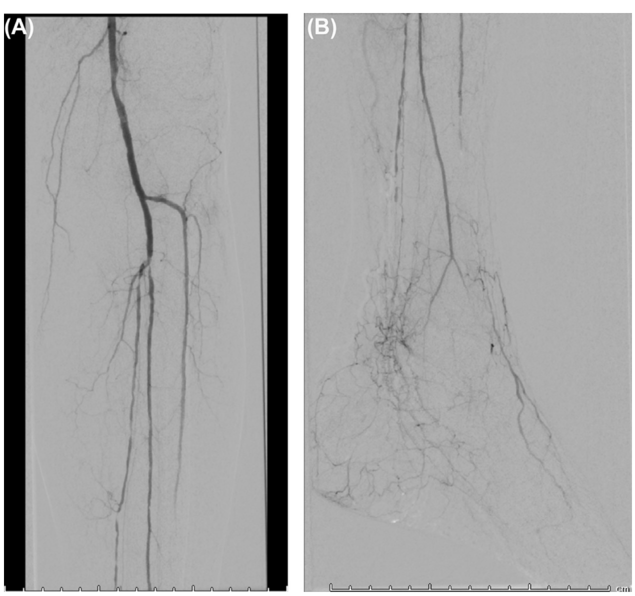

Figure 3. Selective digital subtraction angiography from the popliteal artery, left leg. (A) Antero-posterior view below the knee. (B) Lateral view of the foot. (A) Inflow shows a moderate popliteal stenosis. (A) The anterior tibial has a stenosis at origin with mid-vessel occlusion (B) and some reconstitution of the dorsalis pedis in the foot. (A) Peroneal origin stenosis with moderate multilevel disease; (B) the peroneal artery is then the best vessel at the ankle but with minimal collateralisation into the foot. (A) Severe posterior tibial artery disease from origin; (B) it occludes above the ankle with no foot arch reconstitution.

Figure 4. Failed re-entry into the dorsalis pedis.

With this in mind, for both endovascular and open surgery, direct angiosomal reperfusion is superior to indirect reperfusion for wound healing (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.39–0.68; $p < .001$) and limb salvage (OR 0.37, 95% CI 0.24–0.58; $p < .001$) (see Table 1). Although the effect size is marginally stronger for open surgery, the difference between direct and indirect revascularisation is more pronounced for endovascular intervention. All case series inherently contain selection bias, and the majority of the endovascular selection bias (direct fails so indirect becomes the default) is highlighted by the clinical case presented.

Endovascular clinical context

The clinical scenario presented is an example of indirect peroneal angiosomal reperfusion of the toes. The patient had a poor outcome in terms of wound healing, then eventually lost his leg, despite a presumably patent angioplasty site based on sustained improvements in pressure readings. This fits with the findings in the literature, but, more importantly, highlights the essential problem with its selection bias; this man could only have an indirect reperfusion because there were no target arteries in the foot. His outcome was therefore always likely to be worse than a patient with a patent foot vessel, who usually has a direct angioplasty or bypass option. If the dorsalis pedis had been very good in this man repeat angioplasty could have been tried, possibly via a retrograde dorsalis pedis

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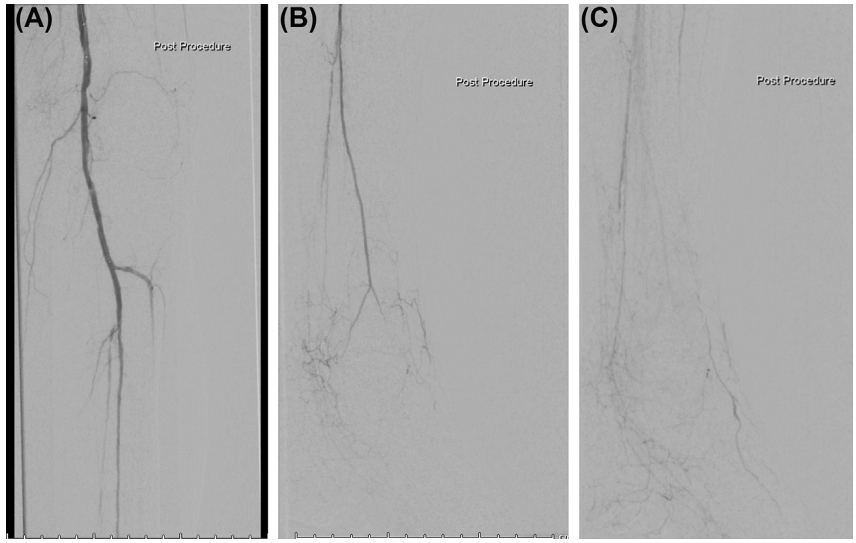

Figure 5. Post-angioplasty angiography. The popliteal and peroneal have been successfully treated by plain balloon angioplasty. (A) The peroneal is now filling preferentially. (B) The distal peroneal also fills preferentially. (C) The short remaining dorsalis pedis does still fill as it did pre-procedure on late angiography, but the foot arch still appears absent.

puncture, or he could have been offered open bypass (or entry into the BASIL 2 randomised trial).[7] The presence of a useable dorsalis pedis would have moved him from the indirect to direct group and he may have fared better, all because of the good runoff vessel rather than an active choice between direct or indirect reperfusion.

When tibial angioplasty was first performed there was a trend towards preserving the best tibial vessel and treating the easy or "safe" vessel (usually the peroneal) leaving the best vessel for bypass if the angioplasty failed. This approach is doomed to failure, and such selection bias may contribute to the results in Table 1, because indirect reperfusion leads to worse outcomes. This is where a balanced decision making process between endovascular and open surgery is so important, because while tibial angioplasty is suitable for the majority of these patients, a strict endovascular first policy may lead to worse outcomes in patients needing open surgery after attempted endovascular intervention.[7]

Combined revascularisation

Another concept for tibial revascularisation is combined revascularisation, i.e., performing direct and indirect revascularisation at the same time. There is little evidence in this area: two case series and a small randomised trial.[5,8,9] The results from both endovascular series are the same, so the results presented here are from the authors own unit.[5]

Essentially, if one can open more than one tibial vessel during tibial angioplasty, the results for amputation free survival are better (adjusted hazard ratio 0.504 [$p = .039$]; Fig. 6).[5] However, the results from combined angioplasty were no better than direct, but were significantly better than indirect after adjusting for confounders. The numbers are low in this series (250 total, only 22 in the combined revascularisation group) and there is inherent selection bias for the same reasons as the clinical case presented; if the patient has the potential to open more than one tibial vessel it is likely that they have better runoff. Nevertheless, it represents the only confounder adjusted series on combined endovascular reperfusion in the literature.

A randomised trial comparing endovascular treatment of one tibial vessel with more than one tibial vessel has been published recently.[8] The set up was subtly different from that comparing combined with direct or indirect because the angiosome was not considered, just the technical ability to open multiple vessels. The foot arch had to be patent for inclusion. However, the results are likely to be biased because there were significantly more direct reperfusions in the group of patients having multiple vessels treated (75% vs. 40%; $p = .004$). There appeared to be no difference when pure angiosomal revascularisation was examined, but the numbers in the trial were too small to adjust accurately for major confounders like this. We can therefore choose whichever story fits our own confirmation bias to explain the results, if we accept that they are accurate. Either direct reperfusion (here more than one tibial vessel) was better than indirect (single vessel), or supply more oxygenated blood to the ischaemic area by opening multiple tibial vessels and get a better result (more on that in the

Table 1. Summary of meta-analysis findings for direct versus indirect angiosomal revascularisation.

	No. of studies (total limbs)	Direct (*n*)	Indirect (*n*)	HG *I*2 (%)	HG *p*	OR (95% CI)	Overall effect *z*	*p*
Wound healing								
All studies	18 (2,998)	1,557	1,441	56	.002	0.51 (0.39–0.68)	4.57	<.001
Endovascular	11 (2,174)	1,147	1,027	61	.004	0.48 (0.34–0.67)	4.30	<.001
Open bypass	8 (865)	482	383	48	.06	0.64 (0.39–1.07)	1.71	.09
Limb salvage								
All studies	20 (3,144)	1,613	1,531	73	<.001	0.37 (0.24–0.58)	4.36	<.001
Endovascular	12 (2,243)	1,158	1,085	81	<.001	0.36 (0.20–0.66)	3.30	.001
Open bypass	8 (866)	482	384	33	.17	0.56 (0.33–0.94)	2.18	.03
Mortality								
All studies	9 (1,213)	641	572	56	.02	0.73 (0.45–1.18)	1.29	.2
Endovascular	3 (303)	151	152	0	.54	1.16 (0.69–1.96)	0.57	.57
Open bypass	3 (237)	138	99	0	.61	0.35 (0.16–0.78)	2.59	.01

Note. Modified from Dilaver *et al.*[6] HG = heterogeneity; OR = odds ratio; CI = confidence interval.

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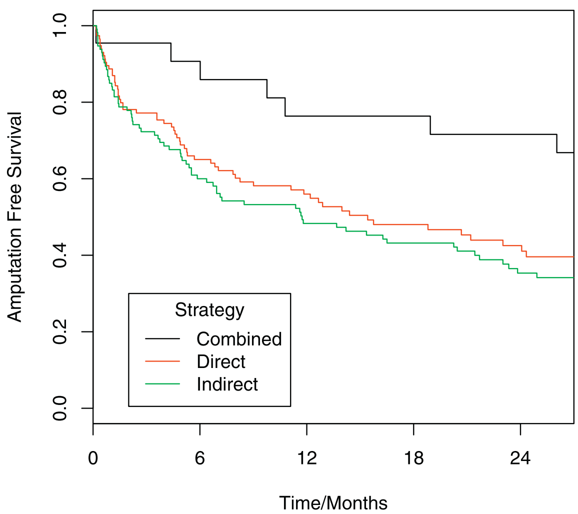

Figure 6. Kaplan–Meier graph comparing amputation free survival in patients undergoing combined approach angioplasty vs. the indirect and direct approaches. Adjusted hazard ratio (AHR) 0.492 ($p = .082$) for combined vs. direct, AHR 0.426 ($p = .037$ for combined vs. indirect. Reproduced from Ambler *et al*.[5]

'Breakdown of the classic angiosome model' section). The aforementioned case series suggest that combined reperfusion (direct and indirect) was no better than direct alone, but the reported results of the trial did not examine this specifically.

Open surgery clinical context

Open surgical bypass is worth considering separately because the outcomes are slightly different to the endovascular group. The significance between direct and indirect reperfusion is lost for wound healing, and diminished for limb salvage and mortality when comparing direct and indirect revascularisation (Table 1).

Again, in the cohort literature there is selection bias because the majority of (now historical) studies with large patient numbers included in meta-analysis offered a bypass first approach for excellent runoff and the presence of a vein for conduit.[1,6] In open surgery the old adage of "restoring in line flow" to the area has always been followed because it seems to be common sense. And common sense prevails here because a direct open operation is superior to an indirect; however, how many surgeons would bypass to a peroneal artery if a posterior or anterior tibial with flow into the foot were available for tissue loss in the foot? Selection bias will again be rife.

Accurately comparing open and endovascular intervention for angiosome specific outcomes is impossible from the literature. However, the comparative results of open and endovascular tibial revascularisation have been contentious enough for the BASIL 2 randomised trial of the endovascular first versus open first approach to tibial intervention to exist and to currently be recruiting.[10]

Breakdown of the classic angiosome model and other concepts

Looking back at the clinical case above and at Fig. 3(B), the angiosome model is not neatly applicable to this man's foot. Even if "direct" reperfusion via the anterior tibial artery was possible, he had no named vessels in his foot supplying the toes, so revascularisation would not be truly direct. This happens commonly in diabetes but it is unclear how important it is when comparing direct and indirect outcomes.

The 'functional angiosome' is the body's response to adapt to ischaemia and has mainly been defined through animal studies.[11] This is when natural interconnections, or choke vessels, between major, named arteries (usually in the foot) dilate in response to ischaemia. While there is no standardised definition, a collateral is the end result of permanent dilation of a choke vessel in response to ischaemia.

This is where imaging studies help clinical decision making. In a recent series of 120 peroneal bypasses, the patency of the foot arch was more important for a good outcome than looking at the "classic" angiosome location of the wound.[12] So we are back to inline flow, even if it's not "direct" in the traditional sense; if the peroneal collateralises into the foot arch as a functional angiosome, to the extent that a distal bypass will run, the patient will do well. However this is not the whole picture because even in angioplasty, which may be successful with no foot arch, direct reperfusion is superior to indirect in diabetic patients with almost no foot vessels remaining.[13]

Perfusion studies tend to show global increases in foot perfusion after tibial reperfusion, whether direct or indirect, with no specific differences in diabetic patients.[14,15] These studies also tend to show a non-angiosomal pattern of ischaemia and reperfusion in critical ischaemia, although they are small series which did not examine this specifically. This implies that it might be most important to supply a greater volume of oxygenated blood to the foot by whatever means, and that because a direct reperfusion is more likely to involve a patient with a patent foot vessel or arch, they fare better after intervention. This also leads to the theory that patients undergoing indirect open bypass may do better than the same patient undergoing indirect endovascular intervention, because the bypass provides a greater volume of blood. There are counter arguments to this: tibial angioplasty only needs to work long enough to heal the wound and can be repeated; the leg is less likely to be lost if a tibial angioplasty occludes than if a bypass occludes, and so on, but all of the arguments for and against are essentially cognitive bias because they are based on inconclusive data.

Summary

So does the evidence support angiosome specific revascularisation? Yes, in the limited way that it is able to, as it supports the commonsense notion of restoring in line flow to the area of ischaemia for the best outcomes. No, in that if you stick rigidly to the old Taylor and Palmer model you will get caught out because what is actually called an angiosome in disease states is debatable. Perfusion studies show that maximising perfusion is key, and this might be via an indirect peroneal reperfusion if this collateralises significantly into the foot arch. Indirect reperfusion without a good

Box 2 Take home messages

- An angiosome is an area of tissue comprising skin, subcutaneous tissue, fascia, muscle, and bone supplied by a specific artery and drained by a specific vein. It was defined in healthy people.
- The angiosome literature for peripheral vascular intervention is low quality and clearly contains bias.
- The "classic" angiosome model may not apply to patients with peripheral vascular disease, especially diabetics.
- Reperfusion via the artery leading directly to the area of tissue ischaemia is more important than sticking to the "classic" angiosome model.
- If feasible, opening multiple arteries endovascularly may be useful provided at least one supplies the ischaemic area directly.
- The angiosome model appears less relevant in open surgery than endovascular intervention.

vessel leading to the ischaemic area may be technically successful as in the case scenario, but will lead to worse outcomes because it is a great example of selection bias in clinical practice and for this reason it is a useful prognostic indicator. Further randomised trials in this area would add little and are potentially harmful, because although the existing literature is biased it can still guide us to the right strategy: target the best vessels with runoff leading to the ischaemic tissue (see Box. 2).

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