Clinical implications of the angiosome model in peripheral vascular disease

Bauer E. Sumpio, MD, PhD,[a] Rachael O. Forsythe, MBChB, MRCS,[b] Kenneth R. Ziegler, MD,[a] Jeff G. van Baal, MD, PhD,[c] Mauri J. A. Lepantalo, MD, PhD,[d] and **Robert J. Hinchliffe, MD, FRCS,[b]**
New Haven, Conn; London, United Kingdom; Almelo, The Netherlands; and Helsinki, Finland

Vascular surgery has seen a revolutionary transformation in its approach to peripheral vascular disease over the last 2 decades, fueled by technological innovation and a willingness by the field to adopt these changes. However, the underlying pathology behind critical limb ischemia and the significant rate of unhealed wounds and secondary amputations despite apparently successful revascularization needs to be addressed. In seeking to improve outcomes, it may be beneficial to examine our approach to vascular disease at the fundamental level of anatomy, the angiosome, to better dictate reperfusion strategies beyond a simple determination of open vs endovascular procedure. We performed a systematic review of the current literature concerning the significance of the angiosome concept in the realm of vascular surgery. The dearth of convincing evidence in the form of prospective trials and large patient populations, and the lack of a consistent, comparable vocabulary to contrast study findings, prevent recommendation of the conceptual model at a wider level for guidance of revascularization attempts. Further well-structured, prospective studies are required as well as emerging imaging strategies, such as indocyanine green dye-based fluorescent angiography or hyperspectral imaging, to allow wider adoption of the angiosome model in vascular operations. (J Vasc Surg 2013;58:814-26.)

Peripheral arterial disease (PAD) is increasing in prevalence worldwide affecting 12% to 20% of the elderly (aged 65 years and older).[1] Critical limb ischemia (CLI) represents the most severe form of PAD and is characterized by rest pain, ulcers, or gangrene.[2] In patients who have progressed to CLI, revascularization of the affected extremity through surgical bypass or endovascular intervention plays a crucial role in staving off limb loss, prolonging survival, and improving their quality of life.[3] Forty percent of patients with CLI who lack revascularization options face the prospect of major amputation within 1 year of diagnosis[4,5]; mortality in these patients may be as high as 20% over this time.[6]

There is evidence to support either bypass surgery or primary angioplasty as first-line treatment modalities for severe and critical limb ischemia.[7] Traditionally, planning for revascularization has utilized the 'best vessel' approach, whereby the target outflow artery is chosen based on technical suitability, disease characteristics, length of bypass required, conduit available, and patent distal vessel to anchor the bypass.[8,9] TASC II suggests that in the case of a femoral tibial bypass, the best vessel, regardless of location, should be used. However, there is increasing interest in the 'angiosome model' of revascularization for ischemic ulceration.[10-12]

The angiosome concept was introduced 25 years ago in a landmark paper by Taylor and Palmer.[13] Utilizing ink injection studies, dissection, perforator mapping, and radiographic analysis of cadaveric specimens, the pair defined the angiosome as a three-dimensional network of vessels not only in the skin, but in all tissue layers between the skin and the bone. The primary supply to the skin was found to come from direct cutaneous arteries, which vary in diameter, length, and density in different areas of the body. These are reinforced by small, indirect vessels that tend to be the terminal branches of arteries that primarily supply the deeper tissues. In the zone between adjacent angiosomes,[14] they identified reduced caliber ("choke") or similar caliber ("true") anastomotic arteries that provide redundant conduits to allow a given angiosome to receive blood flow from an adjacent neighboring angiosome if the source artery is compromised. Ultimately, at least 40 angiosomes in the human body were characterized, with six identified in the foot based on the three main arteries to the foot (Fig 1).[14,15]

ROLE OF DIRECT REVASCULARIZATION OF AN AFFECTED ANGIOSOME

A systematic literature review was undertaken, using search terms including 'angiosome,' 'revascularization,' 'critical AND limb AND ischemia,' and 'direct AND revascularization' (Fig 2). No date limit was set, and all papers were fully accessed. Studies were included if they reported results of the angiosome approach to revascularization of ischemic lower limb ulceration by surgical, angioplasty, or

From the Department of Vascular Surgery, Yale University School of Medicine, New Haven[a]; the Department of Vascular Surgery, St Georges Vascular Institute, London[b]; the Department of Vascular Surgery, Ziekenhuis Groep Twente, Almelo[c]; and the Department of Vascular Surgery, Helsinki Academic Medical Centre, Helsinki.[d]

Author conflict of interest: none.

Reprint requests: Bauer E. Sumpio, MD, PhD, Department of Surgery, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06510 (e-mail: bauer.sumpio@yale.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2013.06.056

Fig 1. The foot and ankle area are divided into six angiosomes, with one angiosome fed by the anterior tibial artery (ATA), three by the posterior tibial artery (PTA), and two by the peroneal artery (PA). The ATA gives rise to the dorsalis pedis artery, supplying the anterior compartment and dorsum of the foot (*pink*). The PTA gives rise to the calcaneal branch, supplying the medial ankle (*black*) and plantar heel (*green*); the medial plantar branch, supplying the medial instep (*yellow*); and the lateral plantar branch, supplying the lateral and plantar forefoot (*blue*). The PA supplies the lateral ankle and plantar heel (*red* and *green overlap*) via the lateral calcaneal artery, and the anterior ankle via its anterior perforator (*pink overlap*). Note the overlap of the heel by both the medial calcaneal branch of the PTA and the lateral calcaneal branch of the PA.

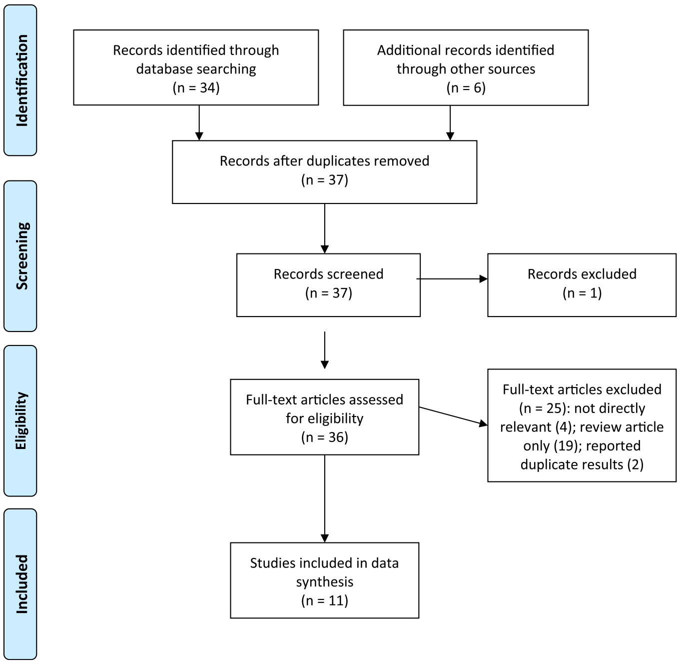

Fig 2. Summary of the article selection process.

Table I. Treatment modality

First author	*Year of publication*	*Country of study*	*Study design*	*Number of limbs (number of patients)*
Neville[25]	2009	USA	Retrospective case series (consecutive patients)	52 (48)
Varela[20]	2010	Spain	Retrospective case series (consecutive patients)	76 (70)
Iida[20]	2010	Japan	Retrospective case series (consecutive patients)	203 (177)
Deguchi[23]	2010	Japan	Retrospective case series	66 (61)
Alexandrescu - SAVES[21]	2011	Belgium	Retrospective case series	26 (25)
Alexandrescu[17]	2011	Belgium	Retrospective case series	232 (208)
Azuma[22]	2012	Japan	Retrospective case series (consecutive patients)	218[a] (228)
Iida[24]	2012	Japan	Retrospective case series (consecutive patients)	369[b] (329)
Soderstrom[19]	2013	Finland	Retrospective case series (consecutive patients)	250 (226)
Kabra[27]	2013	India	Prospective case series	64
Fossaceca[26]	2013	Italy	Retrospective case series	201 (201)

[a]Data from a subset analysis within larger study.
[b]Forty-six patients included in previous study.

hybrid methods. Where study findings were reported in more than one paper, duplicate results were not included.[16] Data was collected on demographic information including relevant comorbidities such as diabetes, end-stage renal disease, and ischemic heart disease and contributing factors such as smoking history and the presence of coexisting neuropathy. End points included limb salvage, wound healing, mortality, technical success, reintervention rate, time to ulcer healing, and major and minor amputation. In studies that compared the use of the angiosome-based direct revascularization (DR) with nonangiosome-based indirect revascularization (IR), results were taken to be significant if $P \leq .05$.

Eleven articles were included in the outcomes analysis, involving treatment of 1616 patients and 1757 limbs reported in papers published between 2008 and 2013 (Table I). These studies were either retrospective case series reviews or retrospective reviews of prospectively kept databases. None of the studies were randomized controlled trials. Techniques reviewed included surgical bypass only, primary angioplasty only, hybrid procedures, or both methods analyzed together. Some studies looked at primary revascularization and excluded those patients with previous interventions,[17-20] while others described the angiosome approach when used as a salvage procedure in patients with previously failed attempts at revascularization.[21] Some studies looked retrospectively at the results of patients in whom successful revascularization had been undertaken, recording whether this had been achieved by targeting the source artery supplying the affected angiosome (equivalent to DR) or not.[19,20,22-25] Other studies compared the use of DR or IR in their patient series, recording outcomes of each technique and thereby examining whether DR is technically possible and effective for treatment of lower limb ischemic ulceration and, if so, how it compares with the results of IR.[18,21,26,27]

Patient comorbidities were included in all studies (Table II). Patients with diabetes were included in all studies and were predominant in nine papers (>80% patients with diabetes). Not all studies applied measures to account for confounding factors. Five of 11 studies included information on the topographical location of disease. The most common site of tissue loss was the forefoot, including toes. Clinical assessment of ulceration was

Table I. Continued.

Treatment modality (bypass only, angioplasty only, hybrid, both)	*Procedure type (primary, secondary, etc)*	*Length of follow-up*	*Outcomes assessed (timing of assessments)*
Bypass	Not specified	Not specified	Complete wound healing, time to complete healing, major amputation, mortality (100 days, 200 days)
Both (angioplasty as first-line if possible)	Primary procedure	Median, 427 (175-828) days	Healing time, healing rate, limb salvage, major amputation, overall survival (1, 3, 6 months then every 6 months)
Angioplasty	Primary procedure	Up to 4 years	Limb salvage, influence of run-off on limb salvage (1, 2, 3, 4 years)
Bypass	Not specified	Median, 316 ± 297 (DR) 381 ± 312 (IR) days	Complete wound healing, time to wound healing, major amputation
Hybrid − arteriovenous switch	Unfit for, or previously failed, conventional treatment	Mean, 21.5 (1-62) months	Technical success, patency, limb salvage, wound healing, major amputation (1, 6 months then every 6 months)
Angioplasty	Primary procedure	Mean, 38.6 (1-68) months	Technical success, survival, freedom from amputation, clinical success, patency, wound healing (12, 24, 36 months)
Bypass	Not specified	Up to 24 months	Wound healing rate, limb salvage (12, 24 months)
Angioplasty	Not specified	Mean, 18 ± 16 months	Limb salvage, death, reintervention rate, amputation-free survival, freedom from major adverse limb events, freedom from major amputation
Angioplasty	Primary	Up to 1 year	Ulcer healing rate, limb salvage, survival, amputation-free survival, reinterventions (1 month then every 1-3 months)
Both/hybrid	Not specified	Up to 6 months	Ulcer healing, major amputation, death (1, 3, 6 months)
Angioplasty	Not specified	Median 17.5 ± 12 months	Technical success, partial ulcer healing, complete ulcer healing, restenosis, major amputation, minor amputation, limb salvage, TcPO2 (1, 6, 12 months then every 6 months)

recorded by eight studies using validated systems such as the Rutherford system (in seven studies), Wagner scale (in two studies), the University of Texas Wound Classification System (in one study), and the Fontaine Stage (in one study). Preprocedural measures of perfusion were specified in eight studies, including toe pressure, ankle-brachial pressure index (ABPI), skin perfusion pressure (SPP), or transcutaneous oximetry (tcPO2). The presence of neuropathy was documented in two studies, and presence of infection was documented in four studies, but the definition of these terms was unclear in one study (Table II).

TASC II classification of disease severity was documented in four studies (Table III). Some studies considered only those patients with single crural vessel run-off,[20,27] one looked specifically at isolated below-the-knee lesions,[24] and others at multi-level disease including aorto-iliac lesions.[18] The target artery also varied, and this was not reported consistently between studies. The anterior tibial was the artery that most frequently fed the affected angiosome, as reported in three studies. The posterior tibial artery was most frequently targeted in DR and IR (reported in four studies). The majority of studies did not specify the affected artery in terms of angiographic findings, angiosome-based disease, or the targets used for revascularization.

The clinical outcomes are summarized in Table IV. Ten studies compared DR and IR. Of these, five reported a significant increase in limb salvage rate with DR when compared with IR. Five out of eight studies who reported wound healing rates found a significant increase with DR when compared with IR; however, length of follow-up varied among these studies (Table I). Mean time to healing was not significantly different in DR compared with IR when analyzed by three studies. One study found a significant increase in amputation-free survival in DR when compared with IR (evaluated by three studies[24,26,27]). One study that demonstrated a significant difference in wound healing at 12 months with DR was undertaken by Varela et al,[20] however, this group also looked at the effect of collaterals on revascularization. They further analyzed patients who had undergone ‘IR through collaterals’ (ie, revascularization of a nonfeeding artery that resulted in patent collaterals to the affected area of ischemia), and this group achieved

Table II. Patient comorbidities

First author (year of publication)	*Number of patients*	*Male*	*Diabetes*	*ESRD*	*Smoker*	*Coronary artery disease*	*Hypertension*	*Presence of neuropathy*
Neville (2009)[25]	48	54%	87%	52%	36%	29%	39%	Not specified
Varela (2010)[20]	70	59%	80%	4%	40%	29%	73%	Not specified
Iida (2010)[18]	177	63%	68%	54%	31%	54%	82%	Not specified
Deguchi (2010)[23]	61	78%	100%	59%	Not specified	28%	Not specified	
Alexandrescu (2011) − SAVES[21]	25	72%	100%	57%	Not specified	88%	Not specified	88%
Alexandrescu (2011)[17]	208	71%	100%	42%	47%	85%	86%	84%
Azuma (2012)[22]	218	74%	81%	50%	Not specified			
Iida (2012)[24]	329	68%	73%	63%	27%	58%	78%	Not specified
Soderstrom (2013)[19]	226	64%	100%	39%	21%	64%	76%	Not specified
Kabra (2013)[27]	64	83%	82%	81%	16%	31%	60%	Not specified
Fossaceca (2013)[26]	201	68%	100%	7%	Not specified	32%	62%	Not specified

ABPI, Ankle-brachial pressure index; *ESRD,* end-stage renal disease; *CDC/NHSN,* Center for Disease Control National Healthcare Safety Network; *PSV,* peak systolic velocity; *UTWCS,* University of Texas Wound Classification System.

Table III. Target vessel and technical results

First author (year of publication)	*Methods of revascularization (%)*	*Severity of lesions (TASC II classification)*	*Feeding artery corresponding to tissue loss using angiosome model*			*DR: target vessel for intervention*		
			AT	*PT*	*Per*	*AT*	*PT*	*Per*
Neville (2009)[25]	Tibial bypass (100%)	Not specified	Not specified			50%	27%	23%
Verela (2010)[20]	Angioplasty (46%), bypass to distal popliteal artery or below[a] (54%)	Type B (1%), Type C (7%), Type D (92%)	DR: AT 82%; PT 13%; Per 4% IR: AT 32%; PT 3%; Per 65% $P < .001$; .23; <.001			82%	13%	4%
Iida (2010)[18]	Angioplasty (100%)	Not specified	DR: AT 55%; PT 44%; Pet 2% IR: AT 58%; PT 46%; Per 2%			Aorto-iliac+stent (12%), fem-pop (54%), tibio-per (83%)		
Deguchi (2010)[23]	Paramalleolar bypass (100%)	Not specified	Not specified					
Alexandrescu (2011) - SAVES[21]	Selective ArterioVenous Endoluminal Switch (SAVES) (100%)	Type B (7%), Type C (23%), Type D (69%)	46%	42%	12%	46%[d]	42%	12%
Alexandrescu (2011)[17]	Below-the-knee angioplasty (100%)	Type B (8%), Type C (35%), Type D (57%)	Not specified			25%	68%	7%
Azuma (2012)[g,22]	Distal bypass (100%)	Not specified	Not specified			Crural (63%), pedal (37%)		
Iida (2012)[g,24]	Angioplasty (100%)	TASC D (99%)	Not specified			Multiple targets		
Soderstrom (2013)[g,19]	Angioplasty (100%)	Not specified[f]	Not specified			61%	47%	24%
Kabra (2013)[27]	Bypass (56%), angioplasty (39%), hybrid (5%)	Not specified						
Fossaceca (2013)[26]	Below-the-knee angioplasty	Not specified				41%	35%	24%

AT, Anterior tibial; *DR,* direct revascularization; *IR,* indirect revascularization; *Per,* peroneal artery; *PT,* posterior tibial.
[a]All lesions treated by surgery were TASC-D.
[b]Study only included primary procedures in which direct flow to the foot was achieved through a single outflow vessel and remained patent during follow-up without reintervention.
[c]Included only patients with successful revascularization: 'obtaining flow from more than one vessel to the pedal arch without surgical bypass.'
[d]Venosomes were targeted in this series.
[e]Failure = vessel could not be reopened, mostly in TASC-D lesions.
[f]Angioplasty not performed in patients with TASC-D lesions unless unsuitable for bypass.
[g]Results are shown for propensity matched pairs.

Table II. Continued.

Severity of wounds	*Indication for intervention (all patients with non-healing ulceration)*	*Presence of infection*
Not specified	ABPI <0.3, monophasic waveforms, TcO2 index <0.4	Not specified
UTWCS Grade 3 (50%)	Ulcer >2 weeks duration, ABPI <0.5, monophasic waveforms, toe pressure <50 mm Hg, lack of pedal pulses	53% (according to CDC/NHSN surveillance definition)
Rutherford 5 (71%) or 6 (29%)	Ankle pressure <70 mm Hg, toe pressure <50 mm Hg, SPP <40 mm Hg	Not specified
Rutherford 5 or 6; Wagner 3-4 (69%, complex 31%)	TcPO2 <30 mmHg, failed other attempts at revascularisation	Not specified
Rutherford 6 (all); Wagner 1 (36%), Wagner 2-4 (64%)	Not specified	69% cellulitis >2 cm
Rutherford 5 (62%), Rutherford 6 (38%)	Not specified	
Rutherford 5 (73%) or 6 (27%)	Toe pressure <50 mm Hg, SPP <40 mm Hg	39% on antibiotics
UTWCS Grade 3 (55%)	ABPI mean 0.68, toe pressure mean 38 mm Hg	UTWCS stage D (39%)
Rutherford 4 (2%), 5 (84%), 6 (14%)	ABPI mean 0.5	Not specified
Fontaine Stage IV, Rutherford 5 or 6	TcPO2 <30 mm Hg, Doppler evidence significant stenosis (>70% caliber reduction, PSV >4 m/s)	Not specified

Table III. Continued.

IR: target vessel for intervention			*DR: technical success/ primary patency*	*IR: technical success/primary patency*	*DR: reintervention rate*	*IR: reintervention rate*
AT	*PT*	*Per*				
36%	36%	28%	Not specified			
IR attempted after failed DR			N/A[b]			
Aorto-iliac+stent (19%), fem-pop (53%), tibio-per (80%)			N/A[c]			
N/A			Technical success 80%; primary patency 66% at 12 months	N/A	Not specified	N/A
23%	65%	12%	Technical success[c] 79%; primary patency 59% at 12 months	Technical success 82%; primary patency 61% at 12 months	Not specified	
Crural (69%), pedal (31%)			Not specified			
			Not specified			
54%	18%	48%	Not specified		15%	17%
			Overall 95% technical success		10% re-angioplasty within 12 months	18% re-angioplasty within 12 months

Table IV. Outcomes

First author (year of publication)	*Number of limbs with DR (%)*	*Number of limbs with IR (%)*	*Limb salvage*			*Wound healing rate complete healing*[a]		
			DR	*IR*	P *value*	*DR*	*IR*	P *value*
Neville (2009)[25]	27 (51)	25 (49)	Not specified			91%	62%	.03
Verela (2010)[20]	45 (59)[b]	31 (41)	93% at 24 months	72% at 24 months	.02	92% at 12 months	73% at 12 months	.008
Iida (2010)[18]	118 (58)	85 (42)	86% at 12 months	69% at 12 months	.03	Not specified		
Deguchi (2010)[23]	30 (45)	36 (55)	Not specified			73%	72%	.43
Alexandrescu (2011) – SAVES[21]	26 (100)	0 (0)	73% at 12 months	N/A	N/A	54%	N/A	
Alexandrescu (2011)[17]	134 (64)	98 (47)	90% at 12 months	84% at 12 months	.035	73%	69%	.018
Azuma (2012)[c,22]	48 (50)	48 (50)	97.8%	92.3%	.855	Not specified		.185
Iida (2012)[c,24]	118 (50)	118 (50)	82%	68%	.01		Not specified	
Soderstrom (2013)[c,19]	84 (50)	84 (50)	86%	77%	.086	72% at 12 months	46% at 12 months	.001
Kabra (2013)[27]	39 (61)	25 (39)	84%	75%	.06	97%	83%	.021
Fossaceca (2013)[26]	167 (83%)[c]	34 (17%)	90% at 17 ± 12 months	91% at 17 ± 12 months	NS	57% complete healing at 12 months	32% complete healing at 12 months	Not specified

DR, Direct revascularization (ie using the angiosome approach); *IR,* indirect revascularization (ie, not using the angiosome approach); *NS,* not significant.
[a]Healing defined as 'complete epithelialization' of wound.
[b]DR was considered gold standard.
[c]All cases had initial attempts at DR; if failure due to chronic occlusion, suboptimal angioplasty, then IR was subsequently carried out.
[d]No significant difference in 'effectiveness' between DR and IR (ie, failure: major amputation, success: limb salvage); χ^2 value 0.02 at 12 months for $\alpha = .05$.
[c]Results are shown for propensity matched pairs.

a similar wound-healing rate to the DR group. They suggest that restoration of blood flow to an area of ischemic tissue via its collaterals, and not necessarily its source artery, is also important. Although limb salvage in this study was higher in DR than IR (93% vs 72%; $P = .02$), it was similar in DR and IR through collaterals (93% vs 88%). Seven studies, with a predominantly diabetic population, reported limb salvage as a primary outcome, and three found a significant increase with DR compared with IR.

DETERMINING THE PERFUSION OF AN ANGIOSOME

One of the critical issues that plague our understanding of the importance of the angiosome model is how a vascular surgeon would determine the perfusion of an affected angiosome in a patient with critical limb ischemia. The studies performed to establish the anatomic basis of the angiosome model were all conducted in cadaveric samples.[13,28-30] In these tissues, perfusion of the arterial system with potentially toxic substances to visualize the arterial branches was limited only by the technical capacity of the investigators. Ink studies, radio-opaque lead oxide dyes, and plastic injection were utilized to determine vascular anatomy and end organ distribution. In living patients, methods utilizing toxic materials and destructive tissue analysis are obviously unavailable and undesirable. An ideal system for angiosome mapping and imaging in the vascular patient would be dynamic, easily utilized in the interventional arena, with the capacity for real-time results and repeatability immediately before and after a revascularization procedure.

The use of ultrasound has also been proposed as a method toward mapping individual angiosomes in specific patients. While the angiosome model holds that the vascular distributions based on a source artery are constant and predictable across all human subjects, the extent of human variability within any given model is well known to all surgeons. Attinger et al suggest that the evaluation of the perfusion to a specific angiosome may be based entirely on physical exam with the assistance of a handheld Doppler device.[15] After identifying an artery supplying a given angiosome (source or collateral) by ultrasound, selective occlusion of the supplying artery above and below the area can reveal the direction of flow. The character of the Doppler signal could also reveal the quality of flow in that segment. Though ultrasound may be useful for mapping known territories, operational planning in vascular surgery – especially in our current era of endovascular intervention – often requires direct visualization of the affected anatomy.

Recent breakthroughs in the use of dye material, laser heat imaging, and angiography may provide the necessary tools to make angiosome-guided revascularization effective in real-time in the interventional setting. For example, Yin et al perfused limbs with a carboxymethyl cellulose/lead oxide injection then imaged by computed tomography angiography and three-dimensional reconstruction.[31] The final product yielded a highly detailed microvascular model that clearly showed the vascular territory, spatial location, distribution pattern, and anastomotic relationships of the cutaneous perforators, as well as the source artery of the

Table IV. Continued.

Mean time to complete healing, days			*Amputation-free survival*			*Major amputation*			*Minor amputation*		
DR	*IR*	P *value*	*DR*	*IR*	P *value*	*DR*	*IR*	P *value*	*DR*	*IR*	P *value*
164.4	159.8	.95	Not specified			9%	38%	NS	Not specified		
71	91	.18	86% at 12 months	85% at 12 months	.70	14% - all diabetic with non-healed wounds			Not specified		
Not specified											
117	120	.95	Not specified			17%	25%	.4	Not specified		
NS	N/A		NS	N/A		23%	N/A		Not specified		
					Not specified						
					Not specified						
Not specified			49% at 4 years	29% at 4 years	.0002	Overall 19%			Not specified		
Not specified			65% at 12 months	61% at 12 months	.36	Not specified					
Not specified						15%	16%	Not specified			
Not specified						10%	9%	NS[d]	34%	62%	NS

main cutaneous perforators. While the direct impact of this work may include the discovery of additional flap pedicles on cadaveric study, the conceptual model may ultimately be translatable to a clinical patient imaging system.

Fluorescent angiography through the use of indocyanine green dye (ICG) holds promise as a method of real-time angiosome visualization in vascular surgery both in and out of the operating room.[32-34] Introduced experimentally in the 1990s, fluorescent angiography came into regular use by plastic surgeons by the mid-2000s. Based on ICG, a dye that absorbs in the near infrared spectrum and emits in the visible spectrum, the intraoperative system relies on a laser that allows immediate visualization of tissue perfusion housed in an imaging camera with a display monitor – a system akin to traditional fluoroscopic angiography. Both ICG and the laser have been proven safe to be used in humans; the low-level laser does not require the use of protective goggles by the operating staff. ICG has the advantages of being excreted exclusively by the liver into the biliary system, allowing for use in renal-compromised patients, having a short half-life (3-5 minutes), being confined to the intravascular compartment due to its plasma protein binding profile, and rarely produces anaphylactic reactions. As ICG contains iodide, its use should be avoided in patients with this sensitivity. Fluorescent angiography is sensitive enough to illustrate small vessels and it has been used to track inflow, outflow, and runoff from a reconstructive flap and its microscopic anastomoses, as well as delineating the borders of angiosomes used in flap design.[35] Whether the adoption of fluorescent angiography in vascular surgery is a viable strategy toward guiding arterial reconstruction has yet to be determined, although preliminary assessments have been promising.[32,33] A worthwhile comparison could be to compare pre- and postrevascularization values within the angiosome concerned in direct and indirect vascularization groups to achieve perfusion data (Fig 3). Certainly, the advantages of real-time assessment of perfusion and intraoperative repeat assessment are attractive features of the system.

Hyperspectral imaging has emerged as another potential tool to allow us to perform real-time assessment of the target angiosome for reperfusion as well as the effectiveness of the arterial reconstruction. Hyperspectral imaging utilizes scanning spectroscopy using wavelengths of visual light to construct spatial maps of tissue oxygenation (Fig 4). Having the advantages of being noninvasive, nonionizing, and noncontact, it has also been shown to detect changes in skin microcirculation in diabetics and to able to predict healing of diabetic foot ulcers with a sensitivity of 86% and specificity of up to 88%. Chin et al found measurable differences in tissue oxygenation of 222 limbs along angiosomal distributions between patients with and without PAD.[36] Measuring deoxyhemoglobin values in the plantar metatarsal, heel, and arch angiosomes, significant differences were found to be correlated not only with PAD status, but severity of PAD as measured by ABPI and Doppler ultrasound waveforms.

With the development of real-time strategies to determine the best target for appropriate revascularization as well as the adequacy of the restored inflow, emerging technologies hold promise in refining surgical and interventional efficacy in vascular surgery, especially when considering the angiosome theory. These technologies

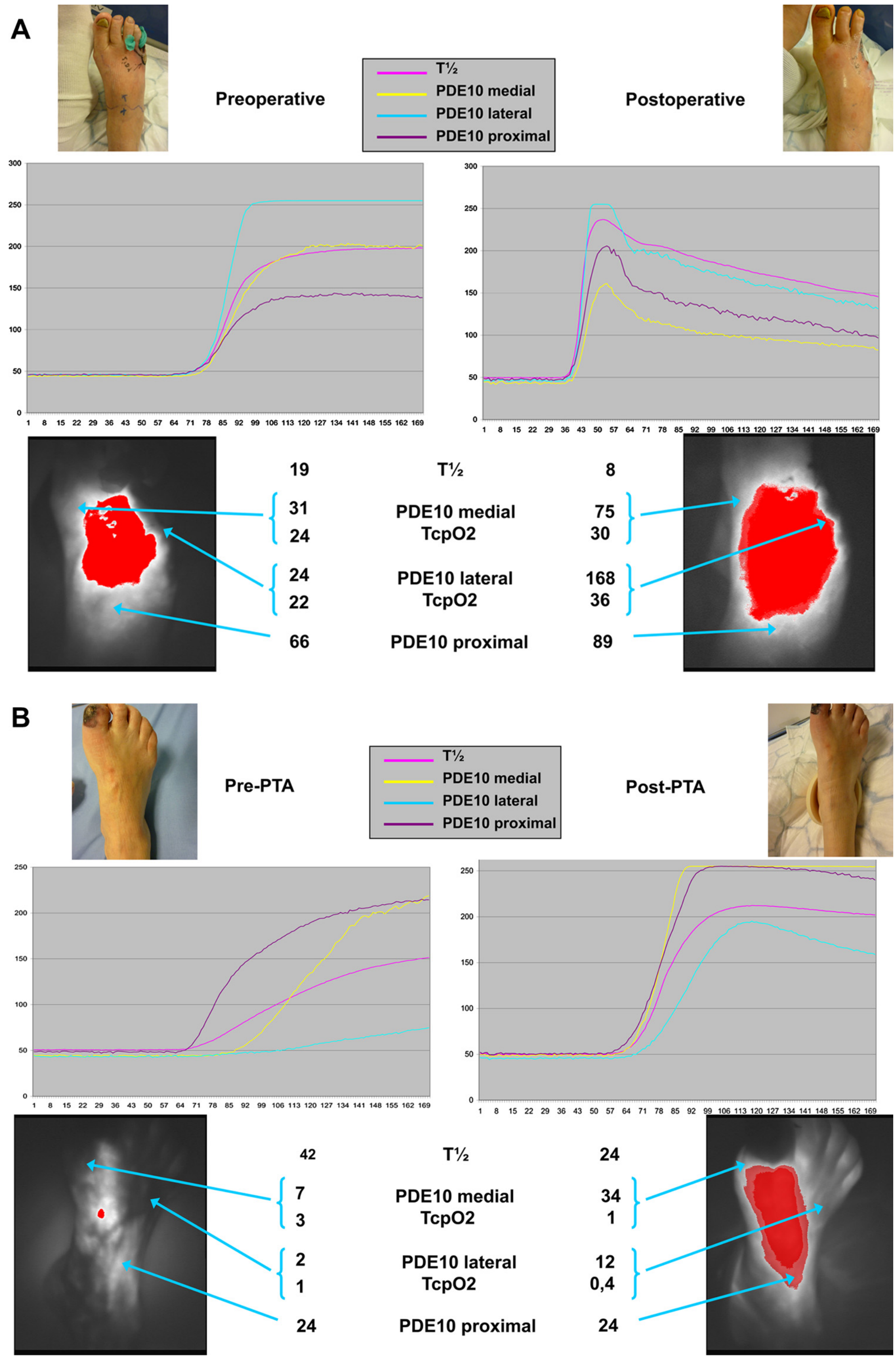

Fig 3. Quantitative assessment of local perfusion using indocyanine green (ICG) fluorescence imaging (Photodynamic Eye, Hamamatsu, Japan). Measurements are made from the video sequence with maximum intensity: **A,** Measurements 1 day before and 1 day after bypass from femoral to distal anterior tibial artery and amputation of 4th and 5th toes. **B,** Measurements 1 day before and 1 day after multilevel PTA on superficial femoral and popliteal artery as well on tibioperonel trunk and peroneal artery. *PTA,* Percutaneous transluminal angioplasty; *PDE10,* fluorescence intensity at 10 seconds from the rising point of the intensity curve, measurements from selected spots of interest (with tcpO2 measurements as reference); *T½,* time to reach the half of the maximum fluorescence intensity.

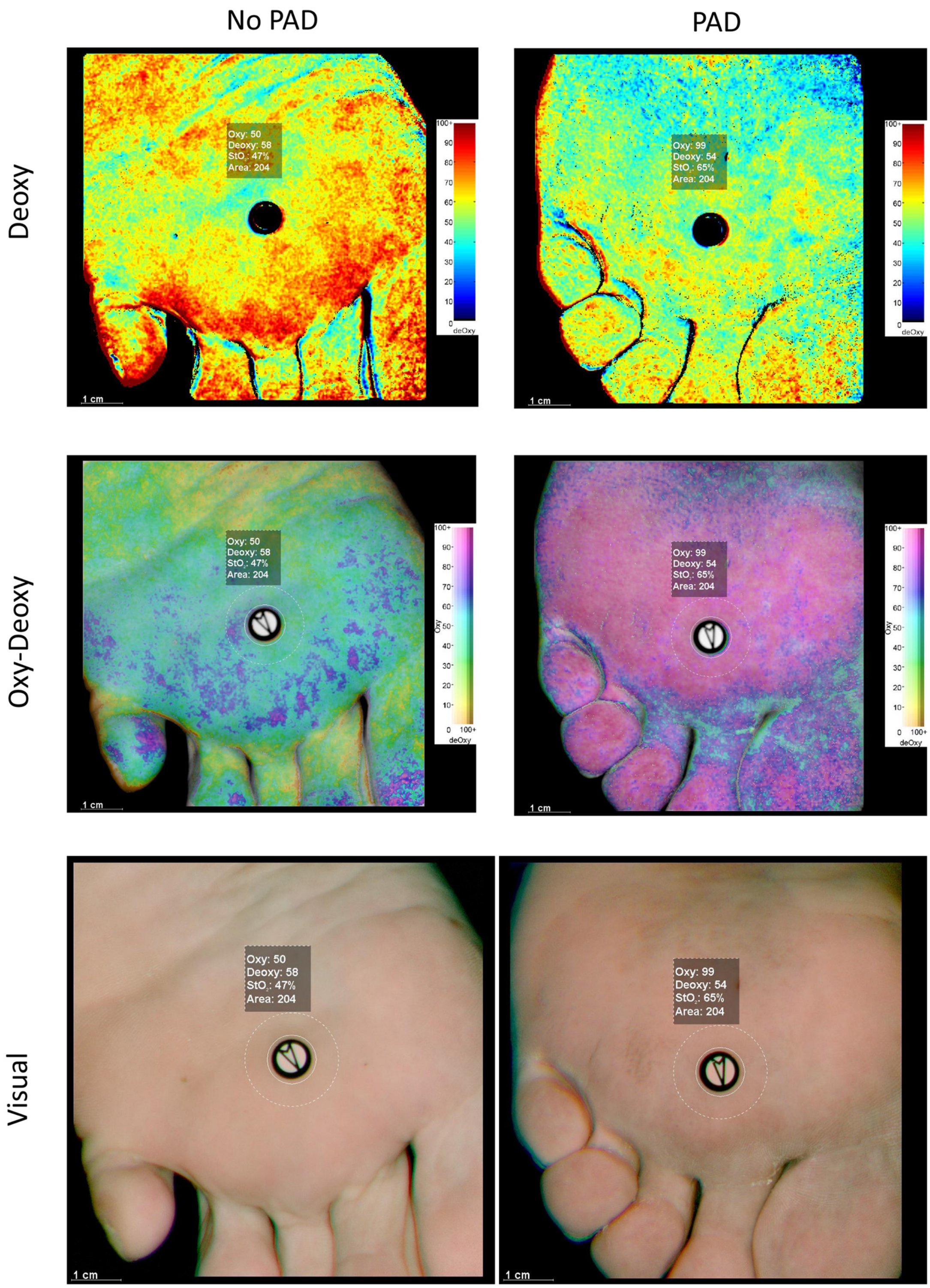

Fig 4. Assessment of plantar angiosome perfusion utilizing hyperspectral imaging. The visual, integrated oxyhemoglobin-deoxyhemoglobin, and only deoxyhemoglobin hyperspectral images are shown of the plantar metatarsal angiosome for a foot with no PAD (*left*) and a foot with PAD (*right*). The foot with PAD demonstrates substantially decreased oxyhemoglobin and deoxyhemoglobin values throughout the angiosome. (Images courtesy of Jason Chin and Melina Kibbe.) *PAD,* Peripheral arterial disease.

appear to fulfill the need for a dynamic, safe, repeatable, and easily used modality for vascular assessment for use in the interventional setting.

DISCUSSION

The gold standard in vascular surgery for critical limb ischemia has traditionally been bypass surgery. For patients in whom bypass was deemed improbable − for example, due to the lack of a target vessel or adequate outflow − advancements in treatment have been made possible with the advent of endovascular interventional techniques in restoring arterial flow.

Contemporary attempts at revascularization are traditionally directed towards the 'best artery' for bypass or angioplasty; however, several modern revascularization series report a rate of unhealed ischemic wounds despite patent bypass or recanalized in-line flow to the foot in up to 18% of cases, leading to a secondary amputation.[8,37,38] These sobering statistics have fueled interest in the angiosome-based strategy, whereby flow is directed to the area of ischemic ulceration via its source artery, rather than focusing on the most suitable artery to be targeted.

Our systemic review of available literature demonstrates that there is limited data available to substantiate an angiosome-based model of revascularization. We were only able to identify five studies that report a significant increase in limb salvage and wound healing when comparing DR with IR. All studies were retrospective and exhibit heterogeneity of patient characteristics and outcomes, precluding accurate comparison, despite attempts to control confounders by propensity score analysis.[19,22] Limitations of the angiosome approach included technical feasibility, reproducibility between centers, and the application of first principles to a heterogeneous population of patients with ischemic ulceration, in particular, those with diabetes and a variable collateral blood supply. Wound healing is slower in patients with diabetes and end-stage renal disease,[39] and there is a tendency for poor collateralization[40] due to the deterioration of small and medium-sized arteries.[13] Furthermore, healing of diabetic foot ulcers is worsened by microvascular dysfunction caused by neuropathy as well as the severity of infection.[41,42] This adds further complexity to the management of ischemic ulceration, particularly when considering targeted treatment of vascular territories. It also underscores the utility of the peroneal artery as target, since it anastomoses via its anterior perforating branch with the anterior lateral malleolar artery of the dorsalis pedis and also to the posterior tibial artery via transverse communicating branches at the level of the Achilles tendon. O'Neal described the 'diabetic end-artery occlusive disease theory,' suggesting that the combination of patchy atherosclerotic lesions, acute septic thrombosis, and destruction of collaterals may explain why irrigation of variable areas of the diabetic foot may rely on a single specific source artery.[43] Perhaps, then, it is even more pertinent to target revascularization to the source artery supplying an area of ischemic ulceration in patients with diabetes, who will have an obliterated collateral network.[28] There is escalating interest in this area.[10,44] However, caution needs to be exercised that direct revascularization attempts into a specific angiosome should not supersede good surgical judgment.

In order to evaluate the angiosome concept of revascularization, larger studies are required. In the first instance, comparison of wound topography and the theoretical angiosome-based targets for revascularization with angiographic patterns of disease may help identify whether it is technically possible to use a DR approach to revascularization in an unselected population. Importantly, the impact of diabetes on collateral supply, specifically the pedal arch, and angiosome boundaries should be documented and explored. Following from this, clinical and technical outcomes of DR vs IR should be evaluated in multicenter studies, with clearly specified standardized outcomes and end points such as wound healing or amputation-free survival.

Finally, it must also be stated that the multi-disciplinary approach, including serial debridement, treatment of sepsis, and risk factors, must also be employed when treating patients with ischemic ulceration.[45] The presence of local neuropathy in patients with diabetes is also an important factor to consider − autonomic denervation contributes to microvascular impairment and impaired wound healing, even in the presence of patent arteries. Adequate control of these factors should be considered imperative. This was variably reported among the studies analyzed.

CONCLUSIONS

The clinical relevance of the angiosome concept may not be fully determined until randomized controlled trials are conducted. Unfortunately, the gold standard of a randomized controlled trial may not be ethical in these patients, as the selection of a distal target in surgical bypass and endovascular therapy must be dictated by best surgical principles, and not by a research directive that would command an inferior intervention. Furthermore, it would be very difficult to build up truly comparative patient groups, and thus any properly planned randomized trial would have a low external value. Thus, more clinical evidence in the form of well-structured, prospective studies must be available before widespread adoption as a novel technique in vascular reconstruction can be advocated.

AUTHOR CONTRIBUTIONS

Conception and design: BS, RH
Analysis and interpretation: BS, JV, ML, RH
Data collection: RF, KZ
Writing the article: BS, RF, KZ, RH
Critical revision of the article: BS, JV, ML, RH
Final approval of the article: BS, JV, ML, RH, RF, KZ
Statistical analysis: RF, RH
Obtained funding: BS
Overall responsibility: BS, RH

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125: e2-220.
2. Novo S, Coppola G, Milio G. Critical limb ischemia: definition and natural history. Curr Drug Targets Cardiovasc Haematol Disord 2004;4:219-25.
3. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5-67.
4. Sumpio BE. Foot ulcers. N Engl J Med 2000;343:787-93.
5. Tang PC, Ravji K, Key JJ, Mahler DB, Blume PA, Sumpio B. Let them walk! Current prosthesis options for leg and foot amputees. J Am Coll Surg 2008;206:548-60.
6. Powell RJ. Update on clinical trials evaluating the effect of biologic therapy in patients with critical limb ischemia. J Vasc Surg 2012;56:264-6.
7. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
8. Lepantalo M, Biancari F, Tukiainen E. Never amputate without consultation of a vascular surgeon. Diabetes Metab Res Rev 2000;16(Suppl 1):S27-32.
9. Sumpio BE, Lee T, Blume PA. Vascular evaluation and arterial reconstruction of the diabetic foot. Clin Podiatr Med Surg 2003;20: 689-708.
10. Alexandrescu V, Soderstrom M, Venermo M. Angiosome theory: fact or fiction? Scand J Surg 2012;101:125-31.
11. Larena-Avellaneda A, Debus S, Pflugradt A, Kolbel T, Diener H. New surgical and hybrid techniques for crural and pedal anastomoses. J Cardiovasc Surg (Torino) 2012;53(1 Suppl 1):151-60.
12. Verzini F, De Rango P, Isernia G, Simonte G, Farchioni L, Cao P. Results of the "endovascular treatment first" policy for infrapopliteal disease. J Cardiovasc Surg (Torino) 2012;53(1 Suppl 1):179-88.
13. Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg 1987;40:113-41.
14. Inoue Y, Taylor GI. The angiosomes of the forearm: anatomic study and clinical implications. Plast Reconstr Surg 1996;98:195-210.
15. Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast Reconstr Surg 2006;117(7 Suppl):261S-93S.
16. Alexandrescu VA, Hubermont G, Philips Y, Guillaumie B, Ngongang C, Vandenbossche P, et al. Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1-4 diabetic foot lesions: practice in a multidisciplinary diabetic limb service. J Endovasc Ther 2008;15:580-93.
17. Alexandrescu V, Vincent G, Azdad K, Hubermont G, Ledent G, Ngongang C, et al. A reliable approach to diabetic neuroischemic foot wounds: below-the-knee angiosome-oriented angioplasty. J Endovasc Ther 2011;18:376-87.
18. Iida O, Nanto S, Uematsu M, Ikeoka K, Okamoto S, Dohi T, et al. Importance of the angiosome concept for endovascular therapy in patients with critical limb ischemia. Catheter Cardiovasc Interv 2010;75:830-6.
19. Soderstrom M, Alback A, Biancari F, Lappalainen K, Lepantalo M, Venermo M. Angiosome-targeted infrapopliteal endovascular revascularization for treatment of diabetic foot ulcers. J Vasc Surg 2013;57: 427-35.
20. Varela C, Acin F, de Haro J, Bleda S, Esparza L, March JR. The role of foot collateral vessels on ulcer healing and limb salvage after successful endovascular and surgical distal procedures according to an angiosome model. Vasc Endovascular Surg 2010;44:654-60.
21. Alexandrescu V, Ngongang C, Vincent G, Ledent G, Hubermont G. Deep calf veins arterialization for inferior limb preservation in diabetic patients with extended ischaemic wounds, unfit for direct arterial reconstruction: preliminary results according to an angiosome model of perfusion. Cardiovasc Revasc Med 2011;12:10-9.
22. Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T. Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the angiosome important in selecting bypass target artery? Eur J Vasc Endovasc Surg 2012;43:322-8.
23. Deguchi J, Kitaoka T, Yamamoto K, Matsumoto H, Sato O. Impact of angiosome on treatment of diabetic ischaemic foot with paramalleolar bypass. J Jpn Coll Angiol 2010;50:687-91.
24. Iida O, Soga Y, Hirano K, Kawasaki D, Suzuki K, Miyashita Y, et al. Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions. J Vasc Surg 2012;55: 363-370.e5.
25. Neville RF, Attinger CE, Bulan EJ, Ducic I, Thomassen M, Sidawy AN. Revascularization of a specific angiosome for limb salvage: does the target artery matter? Ann Vasc Surg 2009;23:367-73.
26. Fossaceca R, Guzzardi G, Cerini P, Cusaro C, Stecco A, Parziale G, et al. Endovascular treatment of diabetic foot in a selected population of patients with below-the-knee disease: is the angiosome model effective? Cardiovasc Intervent Radiol 2013;36:637-44.
27. Kabra A, Suresh KR, Vivekanand V, Vishnu M, Sumanth R, Nekkanti M. Outcomes of angiosome and non-angiosome targeted revascularization in critical lower limb ischemia. J Vasc Surg 2013;57: 44-9.
28. Attinger CE, Evans KK, Mesbahi A. Angiosomes of the foot and angiosome-dependent healing. In: Sidawy AN, editor. Diabetic foot: lower extremity arterial disease and limb salvage. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 341-50.
29. Pan WR, Taylor GI. The angiosomes of the thigh and buttock. Plast Reconstr Surg 2009;123:236-49.
30. Taylor GI, Pan WR. Angiosomes of the leg: anatomic study and clinical implications. Plast Reconstr Surg 1998;102:599-616; discussion: 617-8.
31. Yin ZX, Peng TH, Ding HM, Bai B, Tang ML. Three-dimensional visualization of the cutaneous angiosome using angiography. Clin Anat 2013;26:282-7.
32. Braun JD, Trinidad-Hernandez M, Perry D, Armstrong DG, Mills JL. Early quantitative evaluation of indocyanine green angiography in patients with critical limb ischemia. J Vasc Surg 2013;57:1213-8.
33. Terasaki H, Inoue Y, Sugano N, Jibiki M, Kudo T, Lepäntalo M, et al. A quantitavie method for evaluating local perfusion using indocyanine green fluorescence imaging. Ann Vasc Surg (in press).
34. Zenn MR. Fluorescent angiography. Clin Plast Surg 2011;38: 293-300.
35. Newman MI, Samson MC, Tamburrino JF, Swartz KA, Brunworth L. An investigation of the application of laser-assisted indocyanine green fluorescent dye angiography in pedicle transverse rectus abdominus myocutaneous breast reconstruction. Can J Plast Surg 2011;19:e1-5.
36. Chin JA, Wang EC, Kibbe MR. Evaluation of hyperspectral technology for assessing the presence and severity of peripheral artery disease. J Vasc Surg 2011;54:1679-88.
37. Berceli SA, Chan AK, Pomposelli FB Jr, Gibbons GW, Campbell DR, Akbari CM, et al. Efficacy of dorsal pedal artery bypass in limb salvage for ischemic heel ulcers. J Vasc Surg 1999;30:499-508.
38. Dorros G, Jaff MR, Dorros AM, Mathiak LM, He T. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. Circulation 2001;104:2057-62.
39. Prompers L, Schaper N, Apelqvist J. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747-55.
40. Schaper NC, Nabuurs-Franssen MH, Huijberts MS. Peripheral vascular disease and type 2 diabetes mellitus. Diabetes Metab Res Rev 2000;16(Suppl 1):S11-5.
41. Apelqvist JAP, Lepäntalo MJA. The ulcerated leg: when to revascularize. Diab Metab Res Rev 2012;28(Suppl 1):30-5.
42. Jörneskog G. Why critical limb ischaemia criteria are not applicable to diabetic foot and what the consequences are. Scand J Surg 2012;101: 114-8.

43. O'Neal LW. Surgical pathology of the foot and clinicopathological correlations. In: Bowker JH, Pfeifer MA, editors. Levin and O'Neal's The Diabetic Foot. 7th ed. Philadelphia, PA: Mosby Elsevier; 2008. p. 367-401.
44. Alexandrescu V, Hubermont G. Primary infragenicular angioplasty for diabetic neuroischemic foot ulcers following the angiosome distribution: a new paradigm for the vascular interventionist? Diabetes Metab Syndr Obes 2011;4:327-36.
45. Sumpio BE, Armstrong DG, Lavery LA, Andros G. The role of interdisciplinary team approach in the management of the diabetic foot: a joint statement from the Society for Vascular Surgery and the American Podiatric Medical Association. J Vasc Surg 2010;51:1504-6.

Submitted Feb 27, 2013; accepted Jun 9, 2013.