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Evaluation of the Angiosome Concept Using Near-Infrared Fluorescence Imaging with Indocyanine Green

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Background: The angiosome concept is defined as the anatomical territory of a source artery within all tissue layers. When applying this theory in vascular surgery, direct revascularization (DR) is preferred to achieve increased blood flow toward the targeted angiosome of the foot in patients with lower extremity arterial disease (LEAD). This study evaluates the applicability of the angiosome concept using quantified near-infrared (NIR) fluorescence imaging with indocyanine green (ICG).

Methods: This study included patients undergoing an endovascular- or surgical revascularization of the leg between January 2019 and December 2021. Preinterventional and postinterventional ICG NIR fluorescence imaging was performed. Three angiosomes on the dorsum of the foot were determined: the posterior tibial artery (hallux), the anterior tibial artery (dorsum of the foot) and the combined angiosome (second to fifth digit). The angiosomes were classified from the electronic patient records and the degree of collateralization was classified based on preprocedural computed tomography angiography and/or X-ray angiography. Fluorescence intensity was quantified in all angiosomes. A subgroup analysis based on endovascular or surgical revascularized angiosomes, and within critical limb threatening ischemia (CLTI) patients was performed.

Results: ICG NIR fluorescence measurements were obtained in 52 patients (54 limbs) including a total of 157 angiosomes (121 DR and 36 indirect revascularizations [IR]). A significant improvement of all perfusion parameters in both the directly and indirectly revascularized angiosomes was found (*P*-values between $<0.001-0.007$). Within the indirectly revascularized angiosomes, 90.6% of the scored collaterals were classified as significant. When comparing the percentual change in perfusion parameters between the directly and indirectly revascularized angiosomes, no significant difference was seen in all perfusion parameters (*P*-values between 0.253 and 0.881). Similar results were shown in the CLTI patients subgroup analysis, displaying a significant improvement of perfusion parameters in both the direct and indirect angiosome groups (*P*-values between <0.001 and 0.007), and no significant difference when comparing the percentual parameter improvement between both angiosome groups (*P*-values between 0.134 and 0.359). Furthermore, no significant differences were observed when comparing

The first two authors contributed equally and share first authorship.

Declarations of interest: none.

Funding: This work is co-funded by the PPP Allowance made available by Health ~ Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships; and by the H2020 project Photonics grant agreement id: 871908.

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Ann Vasc Surg 2023; 93: 283–290

https://doi.org/10.1016/j.avsg.2023.01.006

Manuscript received: October 23, 2022; manuscript accepted: January 6, 2023; published online: 13 January 2023

percentual changes of perfusion parameters in directly and indirectly revascularized angiosomes for both endovascular and surgical interventions (*P*-values between 0.053 and 0.899).
Conclusions: This study proves that both DR and IR of an angiosome leads to an improvement of perfusion. This suggests that interventional strategies should not only focus on creating in-line flow to the supplying angiosome. One can argue that the angiosome concept is not applicable in patients with LEAD.

INTRODUCTION

The angiosome concept was first described within the field of reconstructive surgery.[1] The authors defined an angiosome as the anatomical territory of a source artery within all tissue layers. Six angiosomes were identified in the foot, each originating from 3 source arteries and their branches: the anterior tibial artery (ATA), the posterior tibial artery (ATP), and the peroneal artery (AP). In lower extremity arterial disease (LEAD) patients with ischemic wounds, it seems rational to target the revascularization to the angiosome that supplies the site of the ulcer, known as direct revascularization (DR). Several studies, including meta-analyses, showed that angiosome-targeted revascularization increased wound healing.[2–7] In contrast, a study by Rother et al. demonstrated no significant difference comparing the microvascular perfusion improvement after DR or indirect revascularization (IR) using near-infrared (NIR) fluorescence.[8] Furthermore, literature suggests to separate surgical and endovascular interventions, as the angiosome theory might be of greater relevance in the latter.[9] Although frequently investigated, critics consider the clinical applicability of the angiosome theory as debatable as the growth of collateral vessels in the lower extremities will interfere with the borders of the angiosomes. Both Spillerová et al. and Jongsma observed improved wound healing after IR when substantial collateralization was present. For the evaluation of the angiosome concept in vivo, reliable quantification of local tissue perfusion is essential. Different methods have been used to objectify microcirculation, including single-photon emission computed tomography (CT), light guided spectrometry and laser doppler flowmetry.[10,11] NIR fluorescence imaging with indocyanine green (ICG) for the evaluation of tissue perfusion in patients with LEAD seems promising.[12] This technique has already been used for intraoperative guidance in multiple medical fields, including reconstructive and oncologic surgery.[13–16] Furthermore, it has shown promising results in LEAD patients as quality control following revascularization.[15,17–20]

After intravenous administration of ICG, an intravascular fluorophore, the fluorescence intensity can be quantified depicting an in and outflow perfusion pattern of the imaged tissue. Combining ICG NIR fluorescence imaging and the angiosome concept can provide further insight in perfusion patterns following revascularization and guide treatment for patients with LEAD. This study compares preinterventional and postinterventional ICG NIR fluorescence measurements between DR and IR for both endovascular and surgical interventions. Additionally, the effect of collateralization on postinterventional perfusion after IR is evaluated.

METHODS

This prospective cohort study was approved by the Medical Research and Ethics Committee of the Leiden University Medical Center and was performed in a single Dutch Academic Medical Center. Patients classified with Fontaine 2a to Fontaine 4 disease stage who underwent a revascularization procedure between July 2019 and December 2021 were included. DR was defined as an achievement of in-line flow to the corresponding angiosome and IR when in-line flow was not achieved. Collateral grading was performed by 2 independent interventional radiologists. The classification of the collaterals was based on the most recent preprocedural CT angiography and/or catheter angiography. The collateral grade was classified as 'substantial' when collaterals were visible for $\geq$25% of the calf length and/or estimated to be $\geq$ 50% of the corresponding crural artery diameter and/or when objectified as an extensive amount. Preinterventional ankle-brachial index and toe pressure measurements were performed if feasible.

ICG NIR Fluorescence Imaging

Preinterventional and postinterventional ICG NIR fluorescence images of the dorsum of the foot were obtained in accordance with a previously described protocol.[20] ICG NIR fluorescence imaging was performed using the Quest Spectrum Platform® (Quest Medical Imaging, Middenmeer, the Netherlands). Quantification of the measured ICG

NIR fluorescence intensity was performed using the Quest Research Framework (Quest Medical Imaging, Middenmeer, the Netherlands). The quantification software program generated absolute and normalized time-intensity curves out of all regions of interests (ROIs). The method of normalizing the time-intensity curves was in accordance with a formerly described protocol.[21] A total of 10 perfusion parameters were extracted from the time-intensity curves, displayed in Supplemental Figure 1. A postinterventional increase of inflow parameters and decrease of outflow parameters was considered as an improvement of perfusion status.

Angiosome Concept

The ATA from which the dorsalis pedis artery (ADP) originates feeds the complete dorsum of the foot. However, the lateral plantar artery partially feeds the anterior part, the AP the lateral part, and the superficial medial plantar artery the medial part. The ATP supplies the medial ankle and plantar foot consisting out of 2 angiosomes; the lateral and medial plantar angiosome. The lateral plantar artery of the ATP is the most common to feed the hallux. However, the hallux can also be part of the medial plantar angiosome or the dorsalis pedis. The lesser toes are fed by both the lateral plantar angiosome and the dorsalis pedis angiosome with a variability depending on the dominance of the lateral plantar or dorsalis pedis artery. The AP feeds the lateral calcaneal artery which supplies the plantar heel and lateral ankle.[1,22–24] The selected ROIs were based on the angiosome theory: (1) the hallux angiosome classified as supplied by the ATP, (2) The dorsal angiosome supplied by the ADP (ATA) and (3) the lesser toes defined as the combined angiosome (ADP/ATP) (Fig. 1).

Statistical Analyses

Preprocedural and postprocedural perfusion parameters were compared in the DR and IR groups for all patients and in the critical limb threatening ischemia (CLTI) subgroup using the Wilcoxon signed-rank test. Percentual changes of the perfusion parameters preinterventionally and postinterventionally comparing the DR and IR groups for all patients and in the CLTI subgroup was performed using the Mann-Whitney *U* test. A subanalysis based on either endovascular or open surgical revascularization was performed comparing the percentual change of the perfusion parameters after DR and IR using the Mann-Whitney *U* test. Statistical analysis was performed using IBM SPSS Statistics 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.).

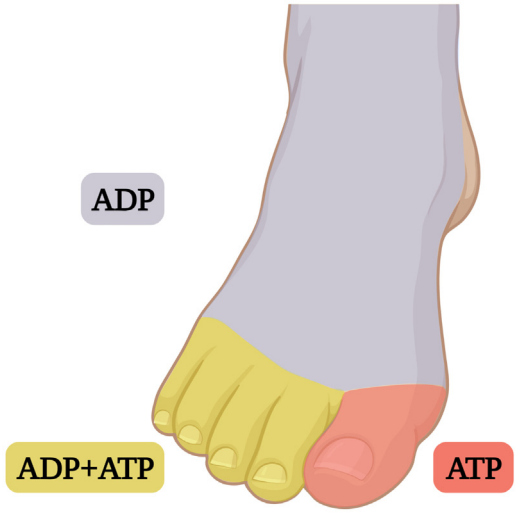

Fig. 1. The classified dorsal angiosomes.

RESULTS

Patient Characteristics

Preinterventional and postinterventional ICG NIR fluorescence imaging was successfully performed in 52 patients (54 limbs), displayed in Table I. Fontaine stage 2a was classified in 6 limbs (11.1%). Fontaine stage 2b was classified in 26 limbs (48.2%) and CLTI considered as Fontaine stage 3 and 4 was classified in 22 limbs (40.7%). Endovascular revascularization was performed in 26 limbs (48.2%) and surgical intervention in 24 limbs (44.4%). A hybrid intervention was performed in 4 limbs (7.4%). Revascularization on femoral and/or popliteal level was performed in 40 limbs (74.1%) and 12 limbs were treated on aortoiliac level (22.2%). Two limbs were treated on a crural level (3.7%). A total of 157 angiosomes were identified, of which 121 were directly and 36 were indirectly revascularized. Collateral grading was performed in the IR group consisting of 24 limbs (36 angiosomes). Consensus in collateral grading was achieved in all cases. Significant collaterals were scored in 19 limbs, insignificant collaterals in 3 limbs and unclassifiable collaterals in 2 limbs due to insufficient contrast on preoperative CT angiography imaging and/or missing lower limb angiographic images.

Angiosome Characteristics

Characteristics per angiosome are displayed in Table II. Fontaine stage 2b was classified in the limbs

Table I. Patient characteristics[c]

Characteristics	Total (n = 52, limbs = 54)
Age (years)	70.2 ± 7.5
Female − n(%)	24 (46.2)
Body mass index	25.8 (4.8)
Diabetes − n(%)	15 (28.8)
Active smoking − n(%)	11 (21.2)
Smoking history − n(%)	48 (92.3)
Renal insufficiency − n(%)	1 (1.9)
Hypertension − n(%)	35 (67.3)
Baseline TP (mm Hg)	89.6 ± 42.4[a]
Baseline ABI	0.7 ± 0.3[b]
Fontaine stage−n(%)	
2a	6 (11.1)
2b	26 (48.2)
3	13 (24.0)
4	9 (16.7)
Type of revascularisation−n(%)	
Endovascular	26 (48.2)
Surgical	24 (44.4)
Hybrid	4 (7.4)
Level of revascularisation−n(%)	
Aortoiliac	12 (22.2)
Femoral/popliteal	40 (74.1)
Crural	2 (3.7)
Angiosomes−n(%)	
Total	157
DR	121 (77.1)
IR	36 (22.9)

Abbreviations: TP, toe pressure, ABI, ankle-brachial index, DR, direct revascularization, IR, indirect revascularization.
[a]Obtained in n = 37 limbs.
[b]Obtained in n = 41 limbs.
[c]Plus-minus values are means ± SD.

Table II. Angiosome characteristics

Characteristics	DR (n = 121)	IR (n = 36)
Fontaine stage −n(%)		
2a	17 (14.0)	1 (2.8)
2b	60 (49.6)	18 (50.0)
3	30 (24.8)	8 (22.2)
4	14 (11.6)	9 (25.0)
Type of revascularization− n(%)		
Endovascular	62 (51.2)	14 (38.9)
Surgical	49 (40.5)	20 (55.5)
Hybrid	10 (8.3)	2 (5.6)
Level of revascularization− n(%)		
Aortoiliac	33 (27.3)	3 (8.3)
Femoral/popliteal	84 (69.4)	32 (88.9)
Crural	4 (3.3)	1 (2.8)

of 60 DR angiosomes (49.6%) and 18 IR angiosomes (50.0%) and CLTI was classified in 44 DR and 17 IR angiosomes (36.4% and 47.2%, respectively). Sixty-two DR (51.2%) and 12 IR angiosomes (38.9%) were endovascularly treated. Surgical intervention was performed in 49 DR and 20 IR angiosomes (40.5%, and 55.5%, respectively). Revascularization in the femoral/popliteal area was performed in 84 DR (69.4%) and 32 IR angiosomes (88.9%).

ICG NIR Fluorescence Results

Preprocedural and postprocedural ICG NIR fluorescence parameter values and percentual improvement for the DR and IR groups within all patients are depicted in Table III and within the CLTI subgroup in Table IV. Preinterventional and postinterventional normalized time-intensity curves for the DR and IR groups are displayed in Figure 2. A schematic overview of an endovascular treated patient along with corresponding normalized time-intensity curves is presented in Figure 3.

All postprocedural perfusion parameter values changed significantly compared to the preinterventional values for both the DR (P-values <0.001) and IR groups (P-values between <0.001 and 0.007). A median percentual improvement was observed for all 10 perfusion parameters in both the DR and IR groups. When comparing the percentual improvement of perfusion parameters between the DR and IR groups, no significant differences were shown for all perfusion parameters (P-values between 0.253 and 0.881).

In the CLTI subgroup analysis, the perfusion parameters changed significantly after both DR and IR (P-values between <0.001 and 0.003, 0.004 and 0.007, respectively). No significant difference was shown when comparing the percentual improvement of the perfusion parameters between the DR and IR groups (P-values between 0.134 and 0.359).

Results of the subgroup analysis comparing the percentual improvement of perfusion parameters between the DR and IR groups within the endovascular and surgical procedure subgroups are displayed in Supplementary Table I. In both subgroups, all perfusion parameters displayed positive median percentual improvements and insignificant differences were seen when comparing the percentual improvement between the DR and IR groups (open: P-values between 0.053 and 0.899, endo: P-values between 0.290 and 0.883).

Table III. Preinterventional and postinterventional values and postinterventional percentual improvement of ICG NIR fluorescence parameters

	Direct revascularization			Indirect revascularization			Percentual improvement		
	Pre	Post		Pre	Post		DR	IR	
Parameters	Median (quartiles)	Median (quartiles)	*P*	Median (quartiles)	Median (quartiles)	*P*	Median percentage (quartiles)	Median percentage (quartiles)	*P*
Imax	33.3 (24.9/42.9)	46.0 (31.7/66.1)	<0.001	39.2 (23.7/47.9)	53.8 (41.5/68.7)	<0.001	31.3 (0.6/83.5)	36.4 (17.3/89.7)	0.401
Ingress rate	0.3 (0.2/0.7)	1.1 (0.3/2.4)	<0.001	0.3 (0.1/0.8)	1.2 (0.7/2.4)	<0.001	169.8 (10.0/580.4)	181.9 (76.9/733.1)	0.279
Absolute slope	1.0 (0.5/1.9)	2.6 (1.0/5.1)	<0.001	1.2 (0.4/2.3)	3.2 (1.6/4.6)	<0.001	103.7 (4.6/349.0)	141.0 (50.9/622.5)	0.298
Normalized slope	2.9 (2.1/4.4)	5.5 (3.1/8.4)	<0.001	3.2 (1.7/4.8)	6.1 (3.9/8.4)	<0.001	49.7 (4.9/159.8)	75.8 (27.1/220.3)	0.263
Tmax	105.9 (58.0/150.1)	37.7 (21.8/105.1)	<0.001	93.5 (47.9/174.4)	40.6 (24.7/68.2)	<0.001	41.6 (3.4/72.7)	57.0 (19.4/76.3)	0.253
AUC egress 60	96.3 (93.7/97.5)	91.8 (83.0/96.5)	<0.001	95.8 (89.9/97.3)	92.2 (81.8/96.0)	0.007	2.7 (−0.1/11.2)	3.8 (0.2/11.6)	0.881
AUC egress 120	91.9 (86.3/94.3)	83.6 (74.4/92.8)	<0.001	91.0 (84.2/94.8)	84.7 (72.3/90.0)	0.002	5.8 (0.0/16.6)	7.2 (0.8/16.1)	0.783
AUC egress 180	86.9 (79.3/90.1)	75.9 (64.4/87.4)	<0.001	85.0 (77.3/90.9)	77.9 (65.1/84.4)	0.001	7.9 (0.1/20.3)	10.3 (0.6/19.9)	0.764
AUC egress 240	81.2 (72.7/85.7)	69.9 (58.8/82.5)	<0.001	80.4 (70.8/87.0)	70.6 (59.4/79.6)	0.001	8.6 (0.0/23.7)	13.5 (−0.7/22.6)	0.767
AUC egress 300	75.7 (67.4/81.5)	60.5 (50.1/75.0)	<0.001	76.2 (64.8/83.2)	64.6 (54.7/74.1)	0.001	9.1 (0.0/25.0)	15.6 (−2.2/25.2)	0.698

Imax, maximum intensity; Tmax, time to max; AUC, area under the curve; DR, direct revascularization; IR, indirect revascularization.

Table IV. Preinterventional and postinterventional values and postinterventional percentual improvement of ICG NIR fluorescence parameters in CLTI patients

	Direct revascularization			Indirect revascularization			Percentual improvement		
	Pre	Post		Pre	Post		DR	IR	
Parameters	Median (quartiles)	Median (quartiles)	*P*	Median (quartiles)	Median (quartiles)	*P*	Median percentage (quartiles)	Median percentage (quartiles)	*P*
Imax	33.1 (25.3/43.0)	49.4 (32.7/60.7)	<0.001	40.2 (23.5/48.2)	55.2 (41.2/73.1)	0.006	22.5 (−2.5/91.6)	36.7 (12.7/138.9)	0.311
Ingress rate	0.3 (0.2/0.9)	1.3 (0.5/3.1)	<0.001	0.6 (0.1/1.1)	2.0 (0.8/4.2)	0.007	170.1 (−12.3/721.2)	267.2 (2.6/1912.6)	0.204
Absolute slope	1.1 (0.7/2.3)	3.5 (1.5/5.8)	<0.001	1.7 (0.4/2.6)	4.1 (2.9/6.9)	0.005	125.1 (−4.3/396.8)	142.9 (40.3/877.8)	0.240
Normalized slope	3.3 (2.3/5.6)	7.1 (5.0/10.4)	<0.001	4.1 (1.7/5.6)	7.3 (6.1/9.2)	0.004	82.5 (−4.6/161.5)	79.4 (14.0/353.9)	0.359
Tmax	100.1 (39.9/128.7)	35.5 (17.4/76.5)	0.003	71.2 (47.1/165.3)	26.1 (16.7/52.2)	0.004	52.5 (−3.7/72.4)	71.9 (4.7/88.2)	0.179
AUC egress 60	95.9 (91.7/97.8)	90.3 (79.6/95.4)	<0.001	96.6 (92.3/97.3)	82.2 (76.7/94.3)	0.006	4.2 (−0.4/12.5)	11.2 (1.9/17.3)	0.157
AUC egress 120	91.4 (84.2/94.1)	81.7 (68.2/91.0)	<0.001	91.0 (84.8/94.9)	73.5 (69.3/86.5)	0.006	8.3 (−0.3/18.9)	14.7 (4.5/25.4)	0.157
AUC egress 180	85.5 (77.8/89.7)	71.3 (58.5/80.0)	<0.001	85.9 (77.6/91.5)	67.5 (62.3/78.6)	0.004	9.7 (0.0/23.7)	17.6 (4.5/29.2)	0.135
AUC egress 240	79.9 (71.3/85.1)	64.3 (51.0/74.8)	<0.001	80.7 (71.3/87.9)	62.0 (56.3/72.3)	0.006	10.9 (0.0/27.0)	19.2 (5.0/32.3)	0.152
AUC egress 300	74.1 (62.5/80.4)	55.9 (40.1/64.8)	<0.001	76.0 (65.6/84.6)	56.5 (51.1/66.8)	0.006	11.6 (0.0/27.9)	21.4 (6.6/34.0)	0.134

Imax, maximum intensity, Tmax, time to max, AUC, area under the curve.

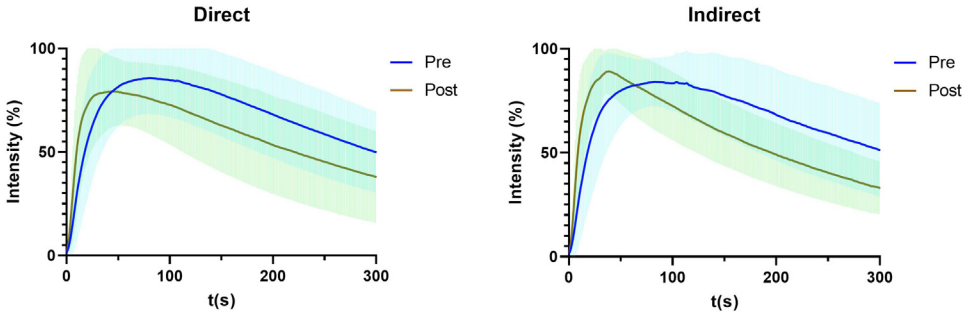

Fig. 2. Preinterventional and postinterventional normalized time-intensity curves for the direct and indirect revascularized angiosome groups displayed as mean with standard deviations.

DISCUSSION

This study shows that perfusion measured with ICG NIR fluorescence significantly increased for both the DR and the IR groups after surgical and endovascular revascularization. Moreover, no difference in the degree of perfusion improvement was found between the DR and IR groups. The same results were seen when solely evaluating patients with CLTI. The significant increase in perfusion after revascularization measured by NIR fluorescence for both DR and IR is in line with the study of Rother et al., which evaluated perfusion changes in bypass surgery patients.[8] Notwithstanding, others have argued that the angiosome concept might be of greater importance in endovascular revascularizations as during bypass surgery the most optimal outflow artery is selected.[2,4] Yet the subgroup analysis in this study displays no significant difference comparing DR and IR in both the surgical and endovascular revascularization subgroups. Several studies investigated the clinical outcome in patients undergoing IR, showing similar clinical results compared to patients undergoing DR in case of present collaterals.[25–27] The high percentage of patients treated with IR and significant collaterals in this study (86.4%), possibly reflecting to the population with LEAD, could therefore explain the significant improvement of perfusion parameters in the IR group. Comparison of perfusion changes using ICG NIR fluorescence in IR patients with and without significant collaterals would be highly relevant; however, it was not feasible in this study due to the limited sample size. Furthermore, the method for grading of collateralization is very heterogeneous in literature. The single-grade scoring system of collaterals in this study was based on 2 articles, which assessed the length, size, and number of collaterals.[28,29] The use of a validated and unambiguous collateral scoring system is preferable for a more accurate future evaluation of this matter. The presence of choke vessels, as demonstrated by Taylor and Palmer in 1987, should also be taken into account.[1] Choke vessels connect adjacent arterial territories and therefore contribute to the variability in angiosomes borders.

In addition, the anatomical variance and predomination of different arteries within patients make it even more complicated to agree on 1 angiosome map.[22,24,30] These major interpatient differences combined complicate the uniform and precise evaluation of the angiosome concept's value in revascularization decision-making. The results of this study are additionally limited by the sole evaluation of dorsal angiosomes and the small amount of crural revascularizations. Another mentionable topic of consideration is the effect of diabetes on the applicability of the angiosome concept. This patient subgroup is known for prolonged wound healing and inferior collateralization compared to nondiabetics, resulting in a potentially increased clinical benefit from DR.[6,31,32] ICG NIR fluorescence is a useful tool to evaluate microvascular perfusion status. As microvascular dysfunction usually occurs in diabetic patients, fluorescence imaging is specifically applicable in evaluation of perfusion for this group.[33–35] This study population was too small for adequate comparison of the perfusion difference between diabetics and nondiabetics. Several reviews have given an overview of the literature on the usefulness of the angiosome concept in procedural decision-making.[3–7] Although DR seems to be of added value in certain clinical situations and patient groups, the included studies were heterogeneous and the quality of evidence was very low, resulting in the recommendation to further investigate the concept's applicability. Perfusion assessment using ICG NIR fluorescence has already proven its

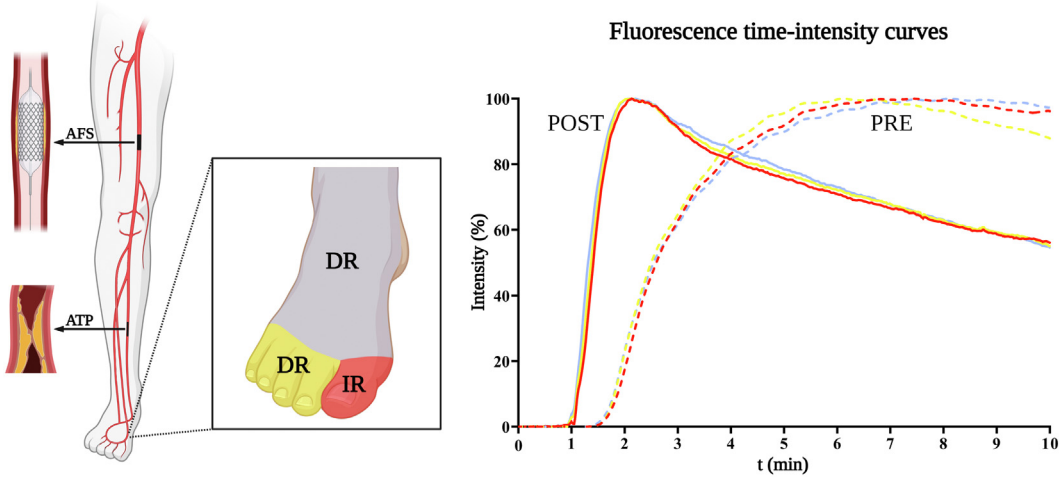

Fig. 3. Overview of an endovascular revascularized AFS patient with an untreated ATP occlusion resulting in 2 direct and 1 indirect treated angiosome. Corresponding preinterventional and postinterventional normalized time-intensity curves are displayed. AFS, arteria femoralis superficialis.

potential as quality control method following revascularization.[15,17–20] Given this potential and the usability for microvascular perfusion assessment, the evaluation of the angiosome concept using ICG NIR fluorescence seems to be of added value as demonstrated in this study. Patients with claudication and CLTI were included in this study, as the main outcome was to compare perfusion changes within DR and IR. However, the angiosome concept is particularly applicable in CLTI patients with wounds as a revascularization could be targeted toward the angiosome in which a wound is located.

Hence, gaining in-line flow to the foot in patients with wounds is reasonably advocated in revascularization guidelines.[36] However, a subgroup analysis in patients with CLTI was performed in this study, which also demonstrated a significant improvement of perfusion in indirectly revascularized angiosomes. Future research is recommended to further evaluate the applicability of the angiosome concept in CLTI patients with the use of ICG NIR fluorescence. We advise that the previously discussed patient-specific factors and other relevant clinical parameters which influence the clinical outcome should be taken into consideration.

CONCLUSION

This study proves that both DR and IR lead to an improvement of microvascular perfusion measured with ICG NIR fluorescence imaging. This suggests that interventional strategies should not only focus on creating in-line flow to the supplying angiosome. One can argue that the angiosome concept is not applicable in patients with LEAD.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.avsg.2023.01.006.

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