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Pilot Assessment of the Angiosome Concept by Intra-operative Fluorescence Angiography After Tibial Bypass Surgery☆

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WHAT THIS PAPER ADDS

To date, ICG fluorescence angiography has been used to examine changes in global limb perfusion. In the present study this method was used for a separate investigation of angiosomal perfusion. This could be a promising approach, as the simplistic angiosome model may be of less relevance when collateralisation can develop over a longer period of time.

Objectives: The "angiosome" concept as a model for decision making in revascularisation of patients with critical limb ischaemia (CLI) has been subject to lively discussion in recent years. The aim of this prospective pilot study was to use intra-operative fluorescence angiography to provide further data on the angiosome concept on the level of microcirculation after tibial bypass surgery.

Design, materials, and methods: This was a prospective analysis of 40 patients presenting with CLI Rutherford stage IV to VI before and after tibial bypass surgery. The macrocirculation was measured by the ankle brachial index. Skin microcirculation was assessed by intra-operative fluorescence angiography. The alteration of microcirculation was compared in direct and indirect revascularised angiosomes. Clinical follow-up investigations were performed and the wound healing rate was compared between the different revascularisation methods.

Results: Cumulated microcirculation parameters showed a significant improvement after surgery (ingress, ingress rate $p<.001$). Likewise, general microcirculatory improvement was observed in each foot angiosome after revascularisation, regardless of the tibial artery revascularised. Furthermore, a comparison of the direct (DR) and the indirect revascularised (IR) angiosomes did not show a significant difference concerning the improvement of microcirculation (difference DR-IR, ingress: 1.69, 95% CI 71.73–75.11; ingress rate: 0.08, 95% CI −12.91 to 13.07). The wound healing rate was similar in both groups, although the time to wound healing was faster by on average 2.5 months in the DR group ($p=.083$).

Conclusion: Microcirculatory improvement was seen over the whole foot after tibial bypass. Therefore, fluorescence angiography is a promising tool to evaluate the angiosome concept in future larger studies. Clinicaltrials.gov: NCT03012750.

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INTRODUCTION

The "angiosome" concept in critical limb ischaemia (CLI) remains a controversial subject in the literature. The concept was initially described by Taylor and Palmer, who found 40 distinctive angiosomes of the human body.[1] Attinger et al. transferred this concept to the chronic ischaemic limb by defining direct and indirect revascularisation of particular angiosomes of the foot affected with ulcer or tissue necrosis.[2] They described six different angiosomes of the foot, each supplied by specific source arteries and veins, originating from the three tibial arteries.

Several retrospective studies have been conducted focusing on the evaluation of this concept, with varying results and study designs.[2–9] Therefore, in recent years four meta-analyses focused on this topic.[10–13] Most found indirect revascularisation (IR) to be inferior to direct revascularisation (DR), particularly in endovascular procedures. Simultaneously, these meta-analyses criticised the low quality of individual studies leading to a low level of meta-analytical evidence. The main sources of potential bias mentioned were the retrospective nature of most individual studies and inappropriate consideration of important co-factors influencing wound

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healing. Thus, new prospective approaches are required to evaluate the relevance of this concept.

In this context perfusion analysis prior to and after revascularisation is seen as an interesting approach, as intact microcirculation has been recognised as a relevant factor for wound healing.[14–16]

A relatively new and promising method, which has already proven feasible in CLI patients, providing not only quantitative but also visual topographic assessment of the microcirculation, is indocyanine green (ICG) fluorescence angiography. Several studies have aimed at investigating global limb perfusion after revascularisation.[17–23]

In patients with long lasting chronic ischaemia of the legs, the relevance of the initially defined angiosome concept is debatable, as wide collateralisation may have occurred. Therefore, the aim of this pilot study was to employ ICG fluorescence angiography to investigate the actual perfusion in both direct and indirectly revascularised angiosomes after tibial bypass surgery.

METHODS

Patients

In this pilot assessment, prospective analysis of 40 consecutive patients (26 men, 14 women) presenting with CLI at Rutherford stages IV to VI, was performed. The mean age was 77 years (range 60–92 years). The data collection was performed prospectively between February 1, 2015 and August 31, 2016. Fluorescence angiography measurements were performed between February 1, 2015 and March 21, 2016. Study termination at which point follow-up investigations ended was August 31, 2016. The median follow-up was 11 months (range 4–18 months). Four patients were lost to follow-up as they did not participate at the follow-up investigation. Therefore, the follow-up index (by August 31, 2016) as defined by von Allmen et al., was 0.88 ($\pm$0.32).[24]

Included were consecutive patients receiving tibial bypass surgery for long segment occlusion with single vessel outflow in the lower leg in a tertiary referral hospital. Exclusion criteria depended solely on the use of iodine based ICG, therefore patients with known allergy against iodine contrast agents were excluded.

The study was conducted in accordance with the Declaration of Helsinki and further approved by the local ethics committee (279_15B) and registered on clinicaltrials.gov (NCT03012750); written informed consent was obtained from all patients. The study results are published in accordance with the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[25]

Study design

In this study the macro- as well as the microcirculation before and after tibial bypass surgery were evaluated. To assess the macrocirculation, measurements of ankle brachial index were made pre- and post-operatively. Patients with falsely elevated indices because of medial sclerosis (ankle brachial index $>$1.3) were excluded from the calculation. Changes in microcirculation resulting from improved macrocirculation after bypass surgery were assessed by intra-operative fluorescence angiography (IFA; SPY Elite, NOVADAQ, Canada). These measurements were performed in the operation room directly prior to the first skin incision and after wound closure of tibial bypass surgery under general anaesthesia; thus a stable circulatory situation was ensured (medium blood pressure 70–90 mmHg, heart frequency 60–80/min, haemoglobin concentration $>$9 g/dl). The room temperature was held constant (21–23°C). Additionally, intra-operative patency assessment of the bypass graft was performed by conventional digital subtraction angiography. To assess the dorsal and the plantar foot angiosomes, both, one dorsal and one plantar measurement per foot were conducted pre- and post-operatively. Each perfusion measurement sequence lasted for 272 s; sequential dorsal and plantar measurements were performed after an interval of 5 min. This interval allowed a sufficient capillary washout of ICG between the dorsal and plantar measurements. For each perfusion sequence a quantity of 0.1 mg ICG per kg body weight was applied intravenously.

In clinical follow-up investigation, the wound status as well as the pain situation of the patients was recorded, the ankle brachial index as well as duplex ultrasound was obtained as a patency assessment of the revascularisation; the wound size was evaluated and documented by photography, wounds were graded at the time of the first investigation employing the Wound, Ischaemia and Foot Infection Score (WIFI Score) from the Society of Vascular Surgery.[26] Following this score, the amputation risk after one year could be predicted. Furthermore, the wound healing time was evaluated for all patients at follow-up. At this point, wound healing was defined as complete epithelialisation. Patients still presenting with wounds at follow-up investigation were defined as non-healing. A comparison was conducted of the time to wound healing and the wound healing rate depending on the revascularisation method (DR and IR).

To address the individual bypass outflow and pedal arch patency as well the individual collateralisation, the intra-operative digital subtraction angiograms were scored according to the pedal arch classification as suggested by Kawarada.[27] Category I was defined as complete pedal arch with a patent dorsalis pedis and plantar artery. Category IIa was characterised as a patent dorsalis pedis artery and an occluded plantar artery, accordingly, Category IIb with a patent plantar and an occluded dorsalis pedis artery. Category III was defined as collateral foot perfusion with no patent pedal vessel.

Technical aspects of intra-operative fluorescence angiography

Fluorescence angiography is an imaging tool for capturing and viewing fluorescence images of tissue perfusion up to a depth of 5–7 mm. There are a variety of fluorescence angiography systems available; in this study, the SPY imaging system (NOVADAQ, Canada) was used, which enables quantitative assessment of the fluorescence sequences.

The system is integrated in a mobile unit, containing a near infrared camera and a data processing unit. For intraoperative use the camera is covered by a sterile coating. Additionally, the camera provides a distance sensor as well as a laser light source.

Use of the SPY imaging system requires intravenous injection of fluorescent dye (indocyanine green), which is then detected after circulation time in the analysed area by the infrared camera. The enhancement, accumulation, and intensity of ICG in the evaluated tissue during the measurement are then displayed as a video sequence by the infrared camera. ICG is a water soluble tricarbocyanine dye that has been widely used for various medical indications.[28] The dye can be safely used in renally insufficient patients as it is metabolised by the hepatobiliary system.

Initially, ICG was used for haemodynamic monitoring of the cardiac output and the liver function.[29] Since 1975, ICG angiography has been implemented as a standard diagnostic tool for retinal perfusion in ophthalmology.[30] In recent years, ICG angiography has been used widely in the fields of plastic and reconstructive surgery, proving helpful for flap design of free tissue transfers.[31–33] The system has been successfully implemented in vascular surgery as well. It has been shown previously that an improvement of the microcirculation after revascularisation in CLI can be assessed quantitatively by this method.[17,19,34]

Analysis of the video sequences

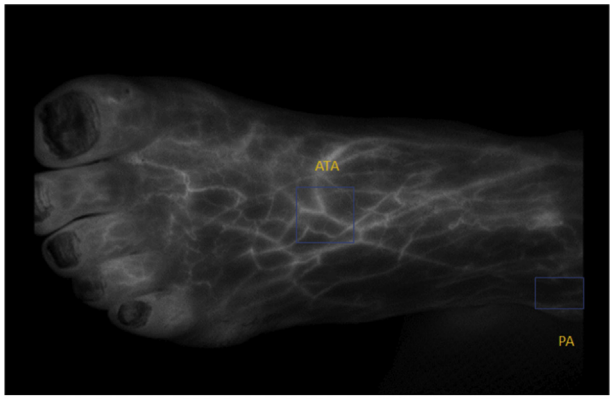
For a subsequent analysis of video sequences, the Spy-Q Analysis Toolkit was used. On the basis of a gray scale with a range of 256 different shades, precise quantification of fluorescence intensity could be established.

Two parameters focusing on the quantification of the fluorescence angiography could be defined: ingress (IN) and ingress rate (InR). IN is calculated as the maximum measured fluorescence intensity subtracted from the lowest fluorescence intensity. As such, it represents the relative enhancement of the fluorescence intensity during one video sequence. The InR represents the increase of fluorescence intensity per second and, therefore, serves as a parameter of the arterial inflow.

As the aim of this pilot study was to compare DR and IR, the fluorescence angiograms of the feet were differentiated in the direct and the indirect revascularised angiosomes; Attinger's definition was applied for definite localisation of particular angiosome zones.

The perfusion parameters were separately analysed in the different areas. Microcirculation of four different angiosomes was evaluated: the dorsum of the foot for the anterior tibial artery (ATA), the lateral ankle for the peroneal artery (PA), and the lateral plantar foot for the lateral plantar artery (LPTA) and the medial plantar foot for the medial plantar artery (MPTA), both arising from the posterior tibial artery (Figs. 1 and 2).

Consequently, angiosomes with the particular feeding tibial artery being used as a recipient vessel in the bypass operation were defined as directly, with the neighbouring angiosomes as indirectly revascularised. Thus, a comparison of the DR and IR was established. In cases where more than one angiosome was defined as DR or IR, the mean values were calculated.

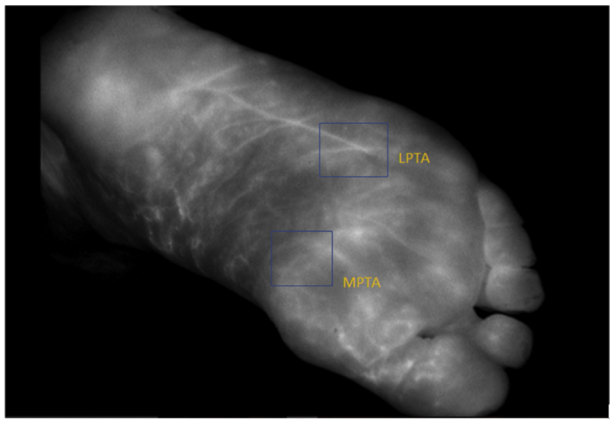


ATA: angiosome of the dorsalis pedis artery, PA: angiosome of the peroneal artery

Figure 1. ICG angiogram of the dorsum of the foot with regions of interest for post-operative evaluation.

Statistical analysis

SPSS 21 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. For parameters exhibiting a symmetrical distribution mean and standard deviation (STD) are given. Slightly skewed distributions of microcirculation parameters meant that descriptive information about central tendency and dispersion of these parameters is provided by the median and the range (minimum — maximum). For assessing changes between pre- and post-revascularisation microcirculation parameters the Wilcoxon signed rank test was applied. Comparisons between independent (sub-) groups were made using the Mann—Whitney *U* test. The comparison of wound healing times was done by the log-rank test. The statistical analysis of the difference between directly and indirectly revascularised angiosomes comprised also an estimation of the effect size for this difference, that is the DR-IR difference of average changes in pre- vs. post-revascularisation microcirculation parameters, with the 95% CI. The statistical significance level was set to $p<.05$ in all analyses.



LPTA: angiosome of the lateral plantar artery, MPTA: angiosome of the medial plantar artery

Figure 2. ICG angiogram of the plantar foot with regions of interest for post-operative evaluation.

Table 1. Patient characteristics.

	Mean	Range
Age, years	76.7	60; 92
Body mass index	28.3	22; 40
	N	%
Sex (♂; ♀)	26; 14	65.0; 35.0
Diabetes [a]	16	40.0
Renal insufficiency [b]	13	32.5
Smoker [c]	14	35.0
Dyslipidaemia [d]	28	70.0
Hypertension [e]	38	95.0

[a] Currently receiving anti-diabetic medication.
[b] Patients at renal insufficiency stages 1–5.
[c] Currently smoking.
[d] Currently receiving lipid reducing medication.
[e] Currently receiving anti-hypertensive medication.

Table 2. Procedure characteristics.

Tibial bypasses (recipient artery)	*N*	%
Anterior tibial artery	17	42.5
Posterior tibial artery	7	17.5
Peroneal artery	16	40.0
Type of bypass		
Great saphenous vein	18	45.0
PTFE	22	55.0
Pre-operative 1 year amputation risk according to WIFI score		
Very low	5	12.5
Low	14	35.0
Moderate	10	25.0
High	11	27.5
Pedal arch classification		
1	5	12.5
2a	20	50.0
2b	10	25.0
3	5	12.5

WIFI = Wound, Ischaemia and Foot Infection Score.

RESULTS

Patients and procedure characteristics

A total of 40 patients were included in the present study (Rutherford stage 4: 12 patients, Rutherford stage 5–6: 28 patients). In 18 patients, the great saphenous vein was used as graft material whereas in 22 cases an artificial graft (PTFE) was necessary because of insufficient or absent vein grafts. The recipient vessel was the anterior tibial artery in 17 cases, the posterior tibial artery in seven cases, and the peroneal artery in 16 cases. Technical success, defined as primary patency of the reconstruction, confirmed by intra-operative conventional digital subtraction angiography with direct flow to the foot, was achieved in all cases. Patients as well as procedure characteristics are shown in Tables 1 and 2, respectively.

Wound healing

The median time to wound healing was 4.25 months. Of the 26 wounds, 17 healed in the follow-up period. As described above, wounds were classified according to their localisation into directly and indirectly revascularised; 14 were categorised as directly and 12 as indirectly revascularised. Eight wounds healed in both groups during the follow-up period, thereby showing no significant difference concerning the wound healing rate (p=.556). However, the comparison of the wound healing time yielded a tendency for a reduced time to wound healing in the directly revascularised wounds (median wound healing time: DR 3.00, IR: 5.50; p=.083).

Assessment of circulation

The macrocirculation evaluated by ABI showed a significant improvement post-operatively (pre 0.40 range 0.00–0.93, post 0.91 range 0.33–1.29, p<.001). Falsely elevated values because of medial sclerosis were excluded from the calculation (n=5).

Microcirculation parameters were assessed by means of IFA. As a first result, the overall perfusion parameters of the cumulated values of the plantar and dorsum of the foot, showed a significant improvement post-operatively (Table 3). Furthermore, the single angiosomes were analysed: all but one angiosome of the foot (ATA, MPTA, LPTA and PA) showed a significant improvement of the microcirculation post-operatively, irrespective of the treated tibial artery. Only for the parameter IN was a negligible non-significant improvement recognised on the lateral ankle for the angiosome of the peroneal artery (Table 3).

As a further result, the directly as well as the indirectly revascularised angiosomes showed a significant improvement post-operatively for both parameters (DR: IN p=.016, InR p<.001; IR: IN p=.001, InR p=.001, Table 4).

To compare DR and IR, the mean values of the differences in improvement of the pre- and post-operative microcirculation parameters were calculated. Very similar improvements were apparent (DR-IR: IN 1.69, 95% CI −71.73 to 75.11, InR 0.08, 95% CI −12.91 to 13.07, see Table 4). Further subgroup analysis was performed for diabetic patients. In this small group (n=16), direct revascularisation tended to show a stronger improvement on the level of microcirculation (DR-IR: IN 12.78, 95% CI −62.27 to 87.83, InR 3.53, 95% CI −3,41 to 17.13, see Table 4).

DISCUSSION

The relevance of the angiosome concept to decision making for revascularisation has been subject to lively discussion in the literature. Several studies, including four meta-analyses, report higher wound healing rates after angiosome targeted revascularisation compared with non-angiosome targeted procedures.[4,6,7,11–13] However, there is evidence that the relevance of the angiosome concept differs between endovascular and surgical revascularisation. As demonstrated by Spillerova et al., wound healing was improved after non-targeted bypass surgery compared with direct endovascular revascularisation.[3,35] Currently, in the guidelines of the European Society for Vascular Surgery for the treatment and diagnosis of peripheral arterial disease, general advice is given for consideration of angiosome directed revascularisation in the CLI patient, which underlines the importance of this

Table 3. Comparison of microcirculation parameters pre- and post-operatively; significance testing by Wilcoxon signed rank test.

	Parameter	Pre median (range)	Post median (range)	*p*-value
Overall	IN	102.00 (0.00–218.00)	140 (23.00–250.00)	<.001
	InR	3.85 (0.00–20.00)	10.85 (0.30–35.70)	<.001
Dorsum	IN	86.00 (0.00–218.00)	145.00 (23.00–250.00)	<.001
	InR	3.30 (0.00–18.60)	10.00 (0.30–24.60)	<.001
Plantar	IN	115.00 (5.00–200.00)	135.00 (35.00–240.00)	.009
	InR	5.80 (0.20–20.00)	11.40 (0.50–35.70)	.001
LPTA	IN	104.00 (5.00–197.00)	120.00 (41.00–194.00)	.011
	InR	3.90 (0.20–22.00)	7.20 (0.90–36.80)	.011
MPTA	IN	85.00 (16.00–183.00)	136.00 (24.00–210.00)	.001
	InR	2.50 (0.20–12.40)	8.00 (0.40–45.30)	<.001
PA	IN	39.50 (4.00–167.00)	40.50 (12.00–135.00)	.224
	InR	0.65 (0.10–8.70)	1.80 (0.10–9.50)	.039
ATA	IN	75.00 (4.00–190.00)	88.00 (20.00–242.00)	.003
	InR	1.00 (0.10–11.40)	4.20 (0.20–33.00)	.001

IN = ingress; InR = ingress rate; ATA = anterior tibial artery; PA = peroneal artery; LPTA = lateral plantar artery; MPTA = medial plantar artery.

Table 4. Comparison of improvement of overall microcirculation between direct (DR) and indirect revascularised (IR) angiosome.

	Change in DR mean (STD)	Change in IR mean (STD)	Difference DR − IR mean (95% CI)	*p*-value
Overall IN	15.85 (36.87)	17.54 (30.78)	1.69 (−71.73 to 75.11)	.823
Overall InR	3.07 (5.43)	2.99 (5.51)	0.08 (−12.91 to 13.07)	.979
Diabetes IN	27.34 (38.54)	14.56 (33.08)	12.78 (−62.27 to 87.83)	.322
Diabetes InR	5.00 (6.48)	1.47 (4.72)	3.53 (−3,41 to 17.13)	.098

IN = ingress; InR = ingress rate.

concept.[36] However, recent literature suggests a differentiation between surgical and endovascular procedures, where this concept might be of higher relevance compared with surgical revascularisation. This is supported by the results of Spillerova et al., and is also in accordance with the findings of the present study.

Interestingly, current literature discusses the definition of angiosome targeted revascularisation in cases when wounds spread over more than one angiosome.[5] Most studies define DR as treating any of the tibial arteries directly supplying the affected angiosome in cases where more than one is possible. Conversely however, Alexandrescu et al. supposed that DR revascularisation is only achieved by treating the posterior tibial artery when the forefoot or the heel is affected.[37] Another problem of the angiosome concept as a standardised model for decision making in CLI is the high inter-individual variability of angiosome distribution. Furthermore, the most important question when considering the clinical adaptability of that concept is the question of feasibility. A group from Helsinki recently showed that angiosome targeted revascularisation would have been possible in up to 80% of cases, with the exact percentage dependent on the chosen definition.[5] Simultaneously, most of the studies analysing and comparing direct and indirect revascularisation do not focus on the relevance of the pedal arch or its collateralisation in the chronic ischaemic foot, which is considered a crucial factor for wound healing in several studies.[38] Thus, even if angiosome targeted revascularisation of the tibial artery has been achieved, it may not necessarily lead to improvement of the microcirculation and safe ulcer healing.

In this context, the present study attempted to gain further insight into changes in the microcirculation following tibial bypass surgery using the IFA method. The IFA technique, although in existence for years, has recently attracted more interest in the field of vascular surgery, as currently available devices ensure quick intra-operative analysis of the video sequences and, as such allow for precise quantification. Using this method, it was demonstrated that there is a significant overall improvement of the perfusion parameters IN and InR of the foot following tibial bypass operation. These results are in accordance with previous findings of the present authors, as well as with results published by others.[17,19] The reproducibility of the IFA technique for the CLI patient was shown by Venermo et al.[20] Previous studies had already confirmed this correlation with established non-invasive methods such as ABI, TBI, and $TcPO_2$.[17,19,20] However, the advantage of IFA is the topographical visualisation of the perfusion of the foot. Thereby, different areas of the foot can be analysed separately, and comparison of the directly and indirectly revascularised angiosomes is possible. Interestingly, the direct and indirect angiosomes both showed significant improvement post-operatively. When comparing these improvements of the microcirculation a very similar magnitude of improvement became apparent between directly and indirectly

revascularised angiosomes. Similar results have already been reported when measuring the immediate changes of tissue perfusion after tibial angioplasty; in these previous studies, the impact of tibial angioplasty on the foot's skin microcirculation was investigated by laser doppler flowmetry and white light tissue spectrometry, with an overall improvement of the foot perfusion identified, but no difference recognised in directly and indirectly revascularised angiosomes.[15]

Interestingly, in the present study, in a subgroup analysis of diabetic patients, the microcirculatory improvement in the directly revascularised angiosomes was elevated in comparison with the indirectly revascularised angiosomes. However, this finding in a small subgroup of 16 patients must be interpreted with caution and requires further evaluation in future larger cohorts, as the impact of the angiosome concept in diabetic patients is debatable.[16,34]

One reason for these findings may be the chronic ischaemic situation of a CLI patient's foot. Long-term chronic ischaemia of the foot is said to promote wide collateralisation at the microcirculation level and intradermal connections between the single angiosomes, so called "choke vessels", may also work as a collateral system on the level of microcirculation. Both could lead to highly variable angiosome borders in CLI patients, as initially described in cadaver studies of non-CLI patients by Taylor and Palmer.[1] Therefore, the present results indicate that an uncritical adaption of the angiosome concept as the main decision making concept in treatment of CLI does not appear applicable in the context of tibial bypass surgery. This study emphasises the relevance of real time tissue perfusion measurements to gain information on the ischaemia grade.

Finally, one major limitation of the study is the limited cohort size. Concerning the wound healing rates, the limited follow-up time in combination with the relatively small number of patients led to a low statistical power for evaluating differences in wound healing between subgroups of the cohort. An assessment of wound healing was not, however, the primary focus of the study; as a result of the highly selected patients with single tibial artery revascularisation, the original model of the angiosome, initially described by injection of pigments in tibial arteries in cadaveric specimens, is best evaluated *in vivo* by selective ICG injection pre- and post-revascularisation, which requires to be proven in further larger studies.

In conclusion, intra-operative fluorescence angiography proved to be feasible for measuring therapy related changes of the microcirculation post-operatively in this pilot study. A general microcirculatory improvement over the whole foot was found after tibial bypass operation. Therefore, fluorescence angiography is a promising tool for evaluation of the angiosome concept in larger future studies.

CONFLICT OF INTEREST

None.

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None.

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