A Systematic Review and Critical Appraisal of Peri-Procedural Tissue Perfusion Techniques and their Clinical Value in Patients with Peripheral Arterial Disease

Wermelink, Bryan; Ma, Kirsten F; Haalboom, Marieke; El Moumni, Mostafa; de Vries, Jean-Paul P M; Geelkerken, Robert H

Published in:
European Journal of Vascular and Endovascular Surgery

DOI:
10.1016/j.ejvs.2021.08.017

Publication date:
2021

Eur J Vasc Endovasc Surg (2021) 62, 896–908

SYSTEMATIC REVIEW

A Systematic Review and Critical Appraisal of Peri-Procedural Tissue Perfusion Techniques and their Clinical Value in Patients with Peripheral Arterial Disease

Bryan Wermelink [a,b,*,‡], **Kirsten F. Ma** [c,‡], **Marieke Haalboom** [d], **Mostafa El Moumni** [e], **Jean-Paul P.M. de Vries** [c], **Robert H. Geelkerken** [a,b]

[a] University of Twente, Multi-Modality Medical Imaging Group, TechMed Centre, Enschede, The Netherlands
[b] Department of Vascular Surgery, Medisch Spectrum Twente, Enschede, The Netherlands
[c] Department of Surgery, Division of Vascular Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
[d] Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands
[e] Department of Surgery, Division of Trauma Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

WHAT THIS PAPER ADDS

Many techniques have been introduced to enable quantification of tissue perfusion in patients with peripheral arterial disease. These techniques should guide the vascular surgeon or interventionalist in real time during the revascularisation procedure and improve clinical outcomes. An overview is given of 10 techniques, focused on study protocols, research goals, and clinical outcomes. Evidence remains low regarding the clinical accuracy of the 10 included techniques, so prospective observational studies, to correlate peri-interventional assessments with clinical outcomes, are necessary as a first step for implementation into daily practice. The technique should be non-invasive, non-operator dependent, accurate, cost effective, and fast.

Objective: Many techniques have been introduced to enable quantification of tissue perfusion in patients with peripheral arterial disease (PAD). Currently, none of these techniques is widely used to analyse real time tissue perfusion changes during endovascular or surgical revascularisation procedures. The aim of this systematic review was to provide an up to date overview of the peri-procedural applicability of currently available techniques, diagnostic accuracy of assessing tissue perfusion and the relationship with clinical outcomes.

Data Sources: MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials.

Review Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines. Four electronic databases were searched up to 31 12 2020 for eligible articles: MEDLINE, Embase, CINAHL and the Cochrane Central Register of Controlled Trials. Eligible articles describing a perfusion measurement technique, used in a peri-procedural setting before and within 24 hours after the revascularisation procedure, with the aim of determining the effect of intervention in patients with PAD, were assessed for inclusion. The QUADAS-2 tool was used to assess the risk of bias and applicability of the studies.

Results: An overview of 10 techniques found in 26 eligible articles focused on study protocols, research goals, and clinical outcomes is provided. Non-invasive techniques included laser speckle contrast imaging, micro-lightguide spectrophotometry, magnetic resonance imaging perfusion, near infrared spectroscopy, skin perfusion pressure, and plantar thermography. Invasive techniques included two dimensional perfusion angiography, contrast enhanced ultrasound, computed tomography perfusion imaging, and indocyanine green angiography. The results of the 26 eligible studies, which were mostly of poor quality according to QUADAS-2, were without exception, not sufficient to substantiate implementation in daily clinical practice.

Conclusion: This systematic review provides an overview of 10 tissue perfusion assessment techniques for patients with PAD. It seems too early to appoint one of them as a reference standard. The scope of future research in this domain should therefore focus on clinical accuracy, reliability, and validation of the techniques.

Keywords: Chronic limb threatening ischaemia, Microcirculation, Peripheral arterial disease, Tissue perfusion
Article history: Received 22 March 2021, Accepted 13 August 2021, Available online 19 October 2021

‡ B. Wermelink and K.F. Ma participated equally should be considered joint first authors.
* Corresponding author. Multimodality Medical Imaging (M3i), TechMed Centre, University of Twente, Drienerlolaan 5, Enschede, 7522 NB, The Netherlands.
E-mail address: b.wermelink@utwente.nl (Bryan Wermelink).

https://doi.org/10.1016/j.ejvs.2021.08.017

INTRODUCTION

In peripheral arterial disease (PAD), macrovascular stenoses or occlusions cause an inadequate blood supply to the lower limbs.[1] Patients with PAD may therefore suffer from intermittent claudication (IC), rest pain, or non-healing wounds, which all lead to an impaired quality of life.[2] IC is the most common presenting symptom of PAD, which in 5% of patients progresses to chronic limb threatening ischaemia (CLTI).[3] To prevent major tissue loss in patients with CLTI, revascularisation is most appropriate.[2] Clinical outcomes after a revascularisation procedure remain unpredictable when current imaging techniques are used.[4] These techniques mainly focus on assessment of the macrovasculature and do not include the assessment of the microvasculature, which is pivotal in patients with CLTI. Therefore, satisfactory results might be accompanied by poor clinical outcomes and early amputations. Ideally, microcirculation changes should be determined during a revascularisation procedure to guide the vascular surgeon or interventionalist on how extensive the procedure must be to improve local tissue perfusion.[5,6] Many invasive and non-invasive techniques have been introduced in recent years that claim to enable the visualisation and quantification of the microvasculature and tissue perfusion. Unfortunately, none of these techniques is currently widely used peri-procedurally. Non-invasive techniques include laser speckle contrast imaging (LSCI), micro-lightguide spectrophotometry (O_2C), magnetic resonance imaging (MRI) perfusion (MRIp), near infrared spectroscopy (NIRS), skin perfusion pressure (SPP), and plantar thermography (PT). Invasive techniques include two dimensional perfusion angiography (2D-PA), contrast enhanced ultrasound (CEUS), computed tomography (CT) perfusion imaging, and indocyanine green angiography (ICGA).

The aim of this systematic review was to provide an up to date overview of the peri-procedural applicability of the aforementioned techniques, a brief description of the techniques, their diagnostic accuracy in assessing tissue perfusion, and their relationship to clinical outcomes.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[7] Eligible articles were included if they described a technique to determine tissue perfusion, in patients with PAD, in a peri-procedural setting. Articles had to have focused on perfusion imaging before and within 24 hours of a revascularisation procedure, to determine the effect of the intervention. Imaging techniques were compared with well known conventional techniques like ankle brachial pressure index (ABPI), toe brachial index (TBI), and clinical outcomes such as wound status, improvement in walking distance, or Fontaine classification. Included articles were full text articles published between 1 January 2010 and 31 December 2020. Exclusion criteria were articles that involved experimental treatment with stem cell therapy, that were not performed peri-procedurally, or that were animal studies. Furthermore, studies with fewer than 10 patients, commentaries, guidelines and letters to the editor were excluded.

Literature search

Four electronic databases were searched for eligible articles: MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials. The database search was performed using medical subject headings (MeSH) terms for “peripheral arterial disease”, “peripheral vascular diseases”, “diagnostic imaging”, “diagnostic techniques, cardiovascular”, “photoacoustic techniques”, “microcirculation”, “perfusion”, “vascular surgical procedures”, and “operating rooms” complemented with the keywords “endovascular technique”, “revascularisation”, and “PTA”. Free text words were used to avoid missing recently published manuscripts without a MeSH label. The complete search strategy is available in Supplementary Appendix 1. The titles and abstracts of the studies were independently screened by two authors (B.W. and K.F.M.), who were blinded to the study authors and journal titles. Disagreements were discussed by the two authors. Articles considered for inclusion were independently reviewed by the same two authors. Disagreements were solved by discussion or by consensus after consulting a third author (R.H.G.).

Data collection

The details of eligible articles were collected by two authors (B.W. and K.F.M.) per study and organised using a predetermined data collection form. Extracted data were grouped per technique and structured regarding characteristics, research goal, comparison with conventional techniques, and clinical outcomes. Technical properties, advantages, disadvantages, and clinical applications of the respective techniques were described. Outcomes of interest comprised clinical applicability of the technique, diagnostic accuracy in assessing tissue perfusion, and their relationship with clinical outcomes. The QUADAS-2 tool was used by two independent observers (B.W. and K.F.M.) to assess the risk of bias and applicability of the studies.[8] This tool was used to assess the risk of bias in patient selection, blinded assessment of the index test from the reference standard, and the flow and timing of the study and its measurements. Patient selection, the index test, and reference standard were assessed for concerns regarding applicability. If there was no mention of a reference standard, the risk of bias of index test and reference standard were scored as

unknown.[8] For techniques reported in an eligible article, the technical background was described and study outcomes are presented in Table 2.

RESULTS

The database searches resulted in 3 910 identified records, of which 569 were duplicates. After title and abstract screening, 3 230 articles were excluded according to the exclusion criteria. Extensive full article review resulted in the exclusion of another 85 articles. Finally, 26 articles, describing 10 techniques, were found to be eligible for inclusion. The study flow diagram is shown in Fig. 1.

Details of the included studies are presented in Tables 1 — 3. Six non-invasive techniques were described in 11 articles including in total 523 patients (Fontaine II — IV). Four invasive techniques were described in 16 articles including in total 653 patients (Fontaine II — IV). Table 1 presents the characteristics of the included studies; Table 2 provides the research goals and clinical outcomes data. Table 3 summarises the advantages and disadvantages of the respective techniques. In two articles,[9,10] two different tissue perfusion techniques were described. The risk of bias and applicability concerns of the included studies according to QUADAS-2 tool are shown in Table 4 and Fig. 2.

Non-invasive techniques

Laser speckle contrast imaging. LSCI uses a coherent laser light to illuminate tissue. This coherent laser light scatters on the surface of tissue, creating an interference pattern called a speckle pattern.[10] The motion of red blood cells (RBCs) in the microcirculation changes the speckle pattern over time, resulting in blurring of the image. Blurring is increased by a higher velocity or number of RBCs and displayed in real time blood flow maps.[10,11]

Magnetic resonance imaging perfusion. MRIp uses arterial spin labelling (ASL) to measure absolute tissue perfusion. ASL uses the inversion of water molecules in blood as an endogenous contrast agent.[12] By subtracting tagged images from a control image, a perfusion signal is obtained.[12] Regions of interest (ROIs) are drawn in muscle groups, from where a perfusion time course is extracted. Thereafter, parameters of interest can be extracted.[12] Other promising MRI techniques do measure tissue perfusion but did not fulfil the inclusion criteria of this review. These techniques are described in more detail in several other studies.[13—15]

Micro-lightguide spectrophotometry. O_2C, or "oxygen to see", uses a combination of laser Doppler flowmetry and spectroscopy. O_2C is determined using white light and laser light, with a penetration depth up to 2 mm reaching the dermis.[16,17] RBC movement causes a laser Doppler shift, which is detected as blood velocity. Spectroscopy is used to determine the amount of haemoglobin in a skin volume. Overall flow can be extracted into the following parameters: oxygen saturation (sO_2); relative haemoglobin (rHB) amount; relative blood flow; and blood flow velocity.[16]

Near-infrared spectroscopy. NIRS measures single tissue oxygen saturation, continuously, with a maximum imaging depth of approximately 15 — 20 mm, including muscle tissue.[18,19] Measurements are performed using an optode, housing the light source (red and near infrared spectrum). Light is emitted through the sampled tissue and is partly absorbed and reflected, which is recorded by photodetectors.[19,20] Oxygenated and deoxygenated haemoglobin have

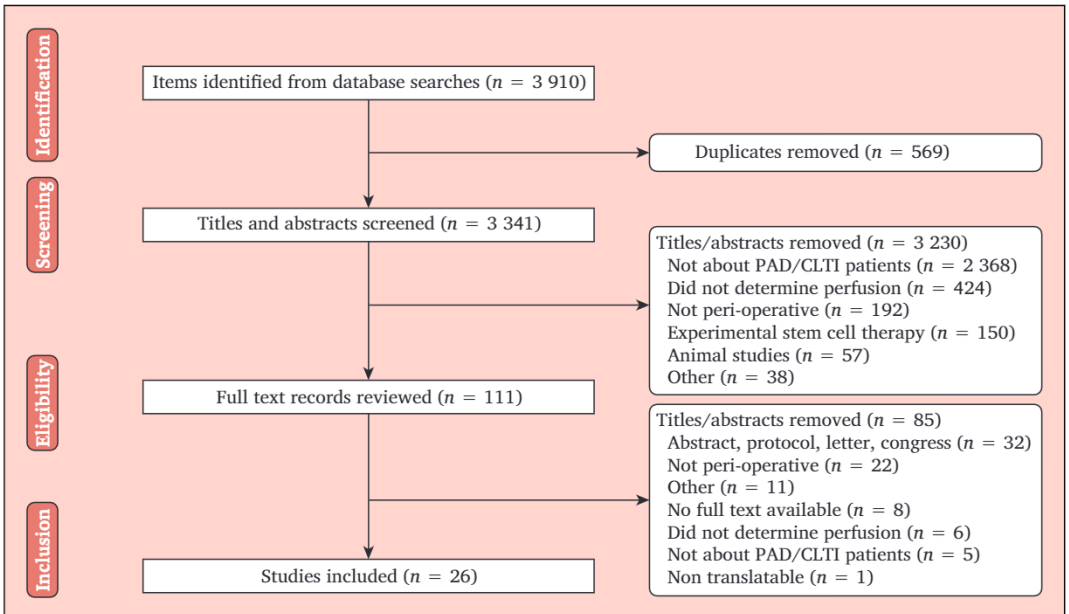

Figure 1. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of screening, eligibility, and inclusion phases of the selection process for studies on peri-procedural tissue perfusion techniques for patients with peripheral arterial disease (PAD) of the lower limbs. CLTI = chronic limb threatening ischaemia.

Table 1. Overview of the 26 included studies for each diagnostic tissue perfusion technique with a focus on study year, study design, number of patients, timing of measurements, measurement protocol, and location and measurement system

Study (year)	Study design	Patients / limbs − *n* (Fontaine)	Timing of measurements	Measurement location	Measurement system
Laser speckle contrast imaging					
Kikuchi *et al.* (2019)[10]	Prospective cohort study	31/33 (7 IIb, 4 III, 22 IV)	Before and immediately after revascularisation	Plantar side of the foot lateral and medial and first and fifth toe	LSFG-PIE (Softcare, Fukuoka, Japan)
MRI perfusion					
Grözinger *et al.* (2014)[12]	Prospective cohort study	10/− (1 IIa, 9 IIb)	Before and after revascularisation	Soleus and tibialis anterior muscle during reactive hyperaemia	3 Tesla system (Magnetom Trio; Siemens Healthcare, Erlangen, Germany)
Micro-lightguide spectrophotometry (O_2C)					
Rother *et al.* (2017)[16]	Prospective cohort study	30/− (8 III, 22 IV)	Continuously during endovascular revascularisation	Dorsal and plantar side of the foot, lateral side of the ankle. Control probe on the contralateral leg	The O_2C (LEA Medizintechnik, Giessen, Germany)
Near infrared spectroscopy					
Boezeman *et al.* (2016)[19]	Prospective cohort study	14/− (6 III, 8 IV)	Continuously during endovascular revascularisation and 4 weeks after treatment	Foot ulcers: 2 cm distal to the arterial ulcer (opt 1) and contralateral (opt 2). Toe ulcers: 2 cm proximal to the arterial ulcer at the distal metatarsal level. Without ulcer: dorsum of the foot (opt 1) and contralateral (opt 2)	Hamamatsu NIRO-200 system (Hamamatsu Photonics K.K, Hamamatsu, Japan)
Kundra *et al.* (2020)[21]	Prospective cohort study	30/− (Unknown)	Continuously during endovascular revascularisation until 12 h after the procedure	The operative limb	Not reported
Plantar thermography					
Chang *et al.* (2020)[22]	Prospective cohort study	124/− (124 IV)	Before and after revascularisation	Dorsal and plantar side of the foot based on the angiosome concept	Digital infrared thermal image system (Spectrum 9000-MB Series; United Integrated Service, Taipei Hsien, Taiwan)
Skin perfusion pressure					
Ichihashi *et al.* (2020)[27]	Prospective multicentre cohort study	147/− (147 IV)	Before and 1, 2, 7, and 30 days after revascularisation	Dorsal and plantar side of the foot based on the angiosome concept	SensiLase PAD 4000 (Kaneka Medical Products, Osaka, Japan)
Ikeoka *et al.* (2018)[25]	Prospective cohort study	16/− (14 IIb, 2 III)	Before and after revascularisation	Dorsal and plantar side of the foot	SPP (Nahri MV monitor; Nexis, Tokyo, Japan)
Ikeoka *et al.* (2020)[9]	Prospective cohort study	33/− (7 IIb, 13 III and 13 IV)	Before and the day after revascularisation	Dorsal and plantar side of the foot	SensiLase PAD 4000 (Vasamed; Eden Prairie, MN, USA)
Kawarada *et al.* (2014)[24]	Retrospective study	44/57 (57 IV)	Before and one day after revascularisation	Dorsal and plantar side of the foot	SensiLase PAD 3000 device (Vasamed)
Kikuchi *et al.* (2019)[10]	Prospective cohort study	31/33 (7 IIb, 4 III, 22 IV)	Before and immediately, three, and seven days after revascularisation	Plantar side of the foot, lateral and medial sides	Laser doppler probe (Philips, Amsterdam, Netherlands)
Mochizuki *et al.* (2016)[23]	Retrospective study	44/48 (5 III, 43 IV)	Before and after revascularisation	Dorsal and plantar side of the foot, ankle, below and above knee	LASER DOPP PV 2000 (Vasamedics, St. Paul, MN, USA)
2D perfusion angiography					
Hinrichs *et al.* (2017)[28]	Retrospective study	21/− (19 IIB, 2 III)	At the start and end of the endovascular procedure	Intra-arterial ROI placement, one proximal and distal to the vascular lesion	Artis Q, (Siemens Healthcare, Forchheim, Germany) and syngo X Workplace VD10A (Siemens Healthcare).
Ikeoka *et al.* (2020)[9]	Prospective cohort study	33/− (7 IIb, 13 III and 13 IV)	At the start and end of the endovascular procedure	ROI was below the ankle and included the arterial foot arch	DSA system not described. 2D perfusion software (Philips Healthcare, Best, the Netherlands)
Jens *et al.* (2015)[30]	Prospective cohort study	18/− (III or IV, exact numbers unknown)	At the start and end of the endovascular procedure	ROI included the region between the tibiotalar joint and the mid-metatarsal region	Allura XperFD20 system with post-processing software, Interventional Workspot R1.1 with 2D perfusion R1 (Philips Healthcare).
Kim *et al.* (2017)[34]	Prospective cohort study	16/− (4 IIb, 3 III, 9 IV)	At the start and end of the endovascular procedure	ROI was a small circular selection overlying the most robust tibial or peroneal artery at the level of the medial malleolus	DSA with 2D perfusion colour coded angiography system. (Philips Healthcare, Andover, MA, USA). 2D perfusion software not described
Murray *et al.* (2016)[29]	Retrospective study	21/− (24 studies: 10 III, 14 IV)	At the start and end of the endovascular procedure	ROI placed over the hindfoot and over the forefoot	Allura Xper FD20 system and postprocessing software from Philips (Interventional Workspot R1.0.1; Philips Healthcare)
Ng *et al.* (2019)[31]	Retrospective study	47/− (8 III, 39 IV)	At the start and end of the endovascular procedure	ROI placed on the main runoff, of the pedal vessel of the foot	Artis zeego and postprocessing software from Siemens (syngo iFlow; Siemens Healthcare)
Pärsson *et al.* (2020)[33]	Prospective cohort study	33/− (11 III, 22 IV)	At the start and end of the endovascular procedure	ROI was manually placed between the tibiotalar joint and the midtarsal region including part of the calcaneus	Allura XperFD20 system with post-processing software (Interventional Workspot R1.0.1; (Philips Healthcare)
Reekers *et al.* (2016)[32]	Prospective cohort study	68/− (unknown)	At the start and end of the endovascular procedure	ROI was placed not lower than the middle cuneiform bone, where the arterial foot arch is situated	Allura XperFD20 system with post-processing software (Interventional Workspot R1.1 with 2D perfusion R1; Philips Healthcare)
Contrast enhanced ultrasound					
Duerschmied *et al.* (2010)[36]	Prospective cohort study	34/− (IIa–IV, exact numbers unknown)	Before and directly after revascularisation and after three and five months of follow up	Area between proximal and medial third of gastrocnemius and soleus muscle	LOGIQ 9 ultrasound system with a 3–7 MHz wide band linear transducer (7L-probe; GE Healthcare Technologies, Milwaukee, WI, USA)

Continued

Table 1-*continued*

Study (year)	Study design	Patients / limbs — *n* (Fontaine)	Timing of measurements	Measurement location	Measurement system
CT perfusion imaging					
Ma *et al.* (2021)[37]	Prospective cohort study	27/— (7 IIb, 11 III, 9 IV)	At the start and within 10 min after endovascular procedure	3 ROIs based on the angiosome concept: dorsum-ATA, plantar surface-PTA, lateral malleolus-PA	Artis Zeego C arm with post-processing via syngo iFlow workstation (Siemens Healthcare)
Indocyanine green angiography					
Colvard *et al.* (2016)[39]	Prospective cohort study	93/— (54 IIb, 3 III, 36 IV)	Before and immediately after revascularisation	Plantar side of the foot	SPY technology (Novadaq Technologies, Bonita Springs, FL, USA)
Mironov *et al.* (2019)[44]	Prospective cohort study	28/— (10 III, 18 IV)	Before and immediately after revascularisation	Dorsal side of the foot	SPY Elite System (Novadaq Technologies, Mississuaga, ON, Canada; LifeCell, Branchburg, NJ, USA)
Patel *et al.* (2018)[40]	Prospective cohort study	47/— (47 IV)	Before and immediately after revascularisation	ROI was the foot ulcer	SPY fluorescent (Novadaq) imaging system
Rother *et al.* (2017)[42]	Prospective cohort study	33/— (10 III, 23 IV)	Before and immediately after revascularisation	Dorsal and plantar side of the foot	SPY Elite system (Novadaq)
Rother *et al.* (2018)[43]	Prospective cohort study	40/— (12 III, 28 IV)	Before and immediately after revascularisation	Dorsal and plantar side of the foot	SPY Elite system (IFA; Novadaq)
Settembre *et al.* (2017)[45]	Prospective cohort study	101/104 (62 IIB, 12 III, 30 IV)	Before and immediately after revascularisation	Dorsal and plantar side of the foot	SPY device (SP 3055; Novadaq)

2D = two dimensional; ROI = region of interest; DSA = digital subtraction angiography; CT = computed tomography; ATA = anterior tibial artery; Opt = optode; PTA = posterior tibial artery; PA = peroneal artery; IFA = intra-operative fluorescence angiography; LSFG = laser speckle flowgraphy; O2C = lightguide spectrophotometry; PAD = peripheral arterial disease; SPP = skin perfusion pressure.

different absorption spectra for red and near infrared light, making it possible to determine the proportion of oxygenated haemoglobin using NIRS. The single tissue oxygen saturation value in the measured tissue therefore reflects the ratio (%) between concentrations of oxygenated and deoxygenated haemoglobin.[19]

Study outcomes

Two studies, including 14 and 30 patients with Fontaine III — IV PAD, respectively, were found. The study by Boezeman *et al.* showed no significant improvement of single tissue oxygen saturation directly after revascularisation.[19] ABPI or TBI showed a significant improvement after four weeks; however, no correlation with single tissue oxygen saturation directly after revascularisation was determined.[19] The study by Kundra *et al.* showed a significant improvement in single tissue oxygen saturation after surgery, which correlated with Doppler signals.[21]

Plantar thermography. Thermography detects infrared radiation, typically emitted from skin, which presents regional temperature as a heat zone image. Both the plantar and dorsal foot are measured using a digital infrared thermal imaging system, with a standardised temperature range of 17°C — 34°C. Software converts the temperature into a colour coded image.[22]

Skin perfusion pressure. SPP can be measured on the dorsal and plantar surface of the foot. A laser Doppler probe placed beneath a blood pressure cuff determines the systolic blood pressure needed to restore the blood circulation in the microcirculation.[9,10,23—27]

Study outcomes

All six SPP studies, including 315 patients, had a cohort ranging from 16 to 147 patients with Fontaine IIb — IV PAD, showed a significantly improved SPP on the dorsal or plantar side of the foot after intervention.[9,10,23—25,27] Ikeoka *et al.* also showed a significant improvement in ABPI and ankle pressure.[25] The studies by Mochizuki *et al.* and Kawarada *et al.* were the only ones with clinical follow up, describing clinical outcomes as major amputation rate and wound healing, demonstrating no differences in SPP values between healed and non-healed limbs.[23,24]

Invasive techniques

Two dimensional perfusion angiography. 2D-PA determines tissue perfusion based on digital subtraction angiography (DSA) images, acquired during endovascular treatment.[9,28—33] ROIs are drawn to determine region specific time attenuation curves (TACs), also called time density curves. A TAC shows a graph comparing contrast intensification against time.[31] From this TAC, a wide range of parameters such as arrival time, time to peak (TTP) and wash in rate can be extracted.[9,28—34] Furthermore, ratios for outflow and inflow can be determined (i.e., $TTP_{outflow}/TTP_{inflow}$), to overcome potential limitations of standardised pump injection.[28] These parameters are used to convert DSA images into colour coded images.

Study outcomes

All eight 2D-PA studies, which included 257 patients, ranging from 16 to 68 patients with Fontaine IIb — IV PAD, showed that an increase in blood flow after revascularisation could be instantly measured and quantified using multiple parameters.[9,28—34] Furthermore, correlations were found between the ABPI, TBI or SPP and 2D-PA parameters.[9,28,34] Murray *et al.* were the only authors who correlated 2D-PA with improvement in Fontaine stage, which showed no significant association.[29]

Table 2. Overview of the 26 included studies for each diagnostic tissue perfusion technique with a focus on aim, main outcomes, follow up period, diagnostic reference standard, and clinical outcomes

Study (year)	Aim	Main outcomes	Follow up period	Diagnostic reference standard	Clinical outcomes
Laser speckle contrast imaging					
Kikuchi *et al.* (2019)[10]	To evaluate whether the new LSFG technology can capture dynamic changes in foot blood flow following surgical revascularisation for PAD	BSSP of the medial and lateral plantar surface significantly increased immediately after the procedure and reached a maximum on d 7 after revascularisation compared with the pre-operative value ($p<.01$)	7 d	No reference standard	No clinical outcomes
MRI perfusion					
Grözinger *et al.* (2014)[12]	To evaluate skeletal muscle microvascular flow in patients suffering from IC before and after successful PTA of the IA or SFA by means of ASL perfusion measurements during reactive hyperaemia	Mean perfusion value increased from 74±52 to 129±80 ($p=.086$) in the soleus muscle and from 53±35 to 111±75 ($p=.041$) in the tibialis anterior. TTP decreased from 59±29 s to 41±14 s ($p=.09$) in the soleus muscle and from 61±24 s to 41±18 s ($p=.045$) in the tibialis anterior	No follow up	Compared with ABPI and pain free walking distance	Mean ABPI increased from 0.56±0.10 to 0.83±0.15 ($p<.001$) Pain free walking distance improved from 86±57 m to no limit in 8 patients; two patients reported a restriction (70 and 500 m, respectively)
Micro-lightguide spectrophotometry					
Rother *et al.* (2017)[16]	To obtain further information on microcirculation changes during tibial revascularisation. Validate and evaluate the relevance of the angiosome concept by means of microcirculation measurements during tibial intervention	Mean sO_2 significant improvement from 45.73% (1.00–95.55%) to 62.39% (2.12–98.04%) ($p<.001$). Overall flow parameter increased significantly from 19.96 AU (0.00–231.9 AU) to 32.01 AU (0.34–224.87 AU) ($p<.001$).	No follow up	Compared with ABPI	Mean ABPI increased significantly from 0.50 (0.31–1.11) to 0.94 (0.50–1.14) ($p<.001$)
Near infrared spectroscopy (NIRS)					
Boezeman *et al.* (2016)[19]	To examine the ability of NIRS to monitor haemodynamic changes in the foot during and after endovascular revascularisation and to investigate the correlation between single StO_2 values and ABPI and TBI	Before revascularisation the mean StO_2 of opt 1 and opt 2 were 51±11% and 57±7%, respectively, and converted to baseline values of 100%. After revascularisation mean StO_2 of opt 1 and opt 2 were 100.4±11.1% ($p=.80$) and 101.8±2.3% ($p=.61$)	4 weeks	Compared with ABPI and TBI values	Mean ABPI and TBI increased significantly after four weeks ($p<.01$). ABPI and TBI values did not significantly correlate with StO_2 values of opt 1 ($p=.55$ and $p=.75$, respectively)
Kundra *et al.* (2020)[21]	To observe the efficacy of NIRS in monitoring regional oxygen saturation and detecting complications in the affected limb and whether it can have a role in predicting a good outcome of the patient operated for CLI	There was significant increase in rsO_2 and limb spO_2 from 27.27±3.92 and 38.13±5.25 to 41.97±1.25 and 58.13±1.64 ($p<.001$) directly after a revascularisation procedure. There was a significant improvement 6 and 12 h after treatment ($p<.001$ and $p<.001$, respectively)	12 h	Compared with Doppler examination	No clinical outcomes
Plantar thermography					
Chang *et al.* (2020)[22]	To investigate whether angiosome based plantar thermography could predict wound healing and freedom from major amputation after EVT in patients with CLI	Mean pre- and post-EVT temperature of the feet was significantly higher in the healing group *vs.* the non-healing group; (30.78°C [range 28.94–32.38]) *vs.* 29.42°C [26.84–31.38]), $p=.015$; and 32.34°C [30.48–33.23] *vs.* 30.96°C [28.74–32.48]), $p=.004$, respectively)	18 mo	Wound healing and freedom from major amputation	No significant difference in the mean pre- and post-EVT temperature of the whole foot between the freedom from major amputation and major amputation groups. Mean post-EVT temperature and derived thermographics were independent predictors for wound healing and freedom of major amputation
Skin perfusion pressure (SPP)					
Ichihashi *et al.* (2020)[27]	To assess SPP changed after EVT and to explore pre-operative factors that affect SPP changes	SPP significantly increased after EVT at the dorsal side from 27.2 (95% CI 25.3–29.2) to 42.5 (95% CI 38.6–46.4) and at plantar side from 27.6 (95% CI 25.7–29.6) to 37.3 (95% CI 33.9–40.8) ($p<.001$).	1 mo	No reference standard	No clinical outcomes
Ikeoka *et al.* (2018)[25]	To clarify the changes in dorsal and plantar SPP of the foot after EVT in patients with diseased SFA	SPP significantly increased after EVT only on the dorsal side from 58.9±20.1 to 79.2±21.6 mmHg ($p=.033$); plantar side: from 72.2±15.4 to 76.3±14.4 mmHg ($p=.54$). The increment of dorsal SPP was significantly larger than that of plantar SPP after EVT ($p=.001$)	No follow up	No reference standard	No clinical outcomes
Ikeoka *et al.* (2020)[9]	To assess the relationship between 2D perfusion analysis and SPPs before and after EVT in patients with BTK occlusive disease	Dorsal SPP increased significantly from 41.0±18 mmHg to 52.2±20 mmHg ($p<.001$) and plantar SPPs were significantly elevated from 49.8±22 mmHg to 57.5±23 mmHg ($p=.006$)	No follow up	Compared with ABPI and systolic ankle pressure	Mean ABPI increased significantly from 0.87±0.14 to 1.03±0.17 ($p<.001$). Mean systolic ankle pressure increased significantly from 120±24 mmHg to 137±24 mmHg ($p=.025$)
Kawarada *et al.* (2014)[24]	To investigate the effect of single tibial artery revascularisation on the dorsal and plantar microcirculation of the foot to clarify the validity of the recent 2D angiosome in the treatment of symptomatic infrapopliteal artery disease	With ATA revascularisation, dorsal SPP increased significantly from 33 (23–40.5) to 52 (32.5–65) mmHg ($p<.001$). With PTA revascularisation, plantar SPP increased significantly from 29.3±9.8 to 43.5±15.9 mmHg ($p<.001$)	Mean follow up time of 17±11 mo	Wound healing, major amputation rate	Wound healing rate was 52.6% and the major amputation rate was 3.5%. Healed limbs had a SPP of 50.0±18.4 (dorsal) and of 45.9±17.6 (plantar) mmHg, and non-healed limbs of 46.8±21.1 (dorsal) and 42.6±19.1 (plantar) mmHg (not significantly different)
Kikuchi *et al.* (2019)[10]	To evaluate whether new LSFG technology can capture dynamic changes in foot blood flow following surgical revascularisation for PAD	SPP showed a significant improvement after revascularisation ($p<.01$).	7 d	No reference standard	No clinical outcomes

Continued

Table 2-*continued*

Study (year)	Aim	Main outcomes	Follow up period	Diagnostic reference standard	Clinical outcomes
Mochizuki *et al.* (2016)[23]	To reveal the effect of blood flow supply to the foot by analysing the SPP values and the pedal arch connection after bypass surgery	Mean SPP value increased significantly on the dorsum of the foot from 22.1±10.8 to 47.3±16.2 ($p<.001$) and from 31.6±16.9 to 56.6±14.7 ($p<.001$) on the plantar surface of the foot	Mean follow up time 25.6±16.1 mo	Limb amputation	During follow up, three patients underwent major amputation. All of demonstrated an increase in SPP after revascularisation
2D perfusion angiography					
Hinrichs *et al.* (2017)[28]	To assess a novel perfusion angiography technique, flow analysis based on two ROIs placed in the treated vessel in patients with PAD	The mean $TTP_{OUTFLOW}/TTP_{INFLOW}$ significantly decreased from 1.81±1.37 to 0.95±0.89 (−52%, $p<.001$). $PD_{OUTFLOW}/PD_{INFLOW}$ (36%) significantly increased from 0.72±0.44 to 0.98±0.43 ($p<.001$). $AUC_{OUTFLOW}/AUC_{INFLOW}$ significantly increased by 69% from 0.69±0.5 to 1.17±0.58 ($p<.001$)	No follow up	Compared with ABPI	The ABPI improved from 0.69±0.16 to 0.96±0.19 (+39%) following the intervention ($p<.001$). No correlation was found between ABPI and 2D perfusion parameters. No correlation analysis with clinical outcomes
Ikeoka *et al.* (2020)[9]	To assess the relationship between 2D perfusion analysis and SPPs before and after EVT in patients with BTK occlusive disease	Only the AT was significantly shortened after EVT in rest from 9.13±3.53 s to 7.26±2.19 s ($p<.001$) and during hyperaemia from 6.15±2.93 s to 4.65±1.46 s ($p=.002$).	No follow up	Compared with ABPI and systolic ankle pressure	Mean ABPI increased significantly from 0.87±0.14 to 1.03±0.17 ($p<.001$). Mean systolic ankle pressure increased significantly from 120±24 mmHg to 137±24 mmHg ($p=.025$). No correlation analysis with clinical outcomes
Jens *et al.* (2015)[30]	To study the feasibility of 2D perfusion imaging in CLI	The AUC increased, but the basic shape stayed unchanged. Density expressed in the height of the peak and the plateau phase was different for each patient. No values reported	No follow up	No reference standard	No clinical outcomes reported
Kim *et al.* (2017)[34]	To determine the feasibility of using the 2D perfusion colour coded angiography to measure haemodynamic changes in the lower extremities after an endovascular intervention inpatients with known PAD	AT decreased significantly from 5.35 to 3.35 s ($p=.003$). Wash in rate increased significantly from 82.81 to 121.9 Si/s ($p=.004$). Width, LTT, TTP, MTT and peak changed significantly after endovascular procedure. Values of these parameters were not described	No follow up	Compared with ABPI	Correlation between the degree of change in 2D parameters (AT, TTP, AUC, peak, wash in rate, width, MTT) and the degree of change in the ABPI was not significant. No correlation analysis with clinical outcomes
Murray *et al.* (2016)[29]	The study examines the clinical feasibility, technical considerations, and initial results of 2D perfusion angiography of the lower limb before and after endovascular interventions	The mean AUC of the hindfoot increased significantly from 4 630±3 760 to 5 993±3 877 ($p=.03$) and in the forefoot from 5 567±3 754 to 7 370±6 350 ($p=.13$). No significant change in TTP or PDV was detected following angioplasty	Short term, exact period not reported	Improvement in clinical stage (Fontaine)	Improvement in clinical symptoms equating to 0.56 grades of the Fontaine stage ($p=.024$). No significant association was detected between improvement in Fontaine stage and an increase in PDV or AUC following angioplasty (Spearman $r=.18$ [$p=.41$] and $r=.08$ [$p=.73$], respectively)
Ng *et al.* (2019)[31]	To evaluate the use of parametric colour coding and analysis of TACs as a real time quantitative measure of perfusion after EVT	Washout phase parameters showed a significant reduction in time required for contrast to decay to a specified percentage after peak ($T_{90\%}$, $T_{80\%}$, $T_{70\%}$, $T_{60\%}$, and $T_{50\%}$). Percentages of contrast decay at specified time intervals after peak (I_{1s}, I_{2s}, I_{3s}, I_{4s}, and I_{5s}) were increased significantly	No follow up	Compared with ABPI and TBI values	Mean ABPI or TBI improved significantly from 0.33±0.26 to 0.62±0.28 ($p<.001$). The percentage of contrast decay 4 s after peak demonstrated the highest correlation coefficient (R ¼=.482) with improvement in ABPI or TBI. No correlation analysis with clinical outcomes
Pärsson *et al.* (2020)[33]	To assess time patterns and dynamics before and after endovascular intervention of stenosis or occlusions in the femoropopliteal and/or infrapopliteal vessels	A significant reduction of mean AT from 3.2 (2.5−4.2) to 2.6 (1.6−3.4) (ø=.007) and mean TTP from 4.1 (2.5−4.2) to 3.1 (2.3 −3.9) ($p=.009$) was observed. MTT significantly reduced from 4.4 (3.8−5.1) to 3.4 (2.7−4.7) ($p=.008$). WI significantly increased from 18.3 (12.6−21) to 30.1 (22 −30.5) ($p=.001$). AUC remained unchanged	30 d	Compared with ABPI and TBI values	Both ABPI and TBI were significantly improved from 0.47±0.19 and 0.21±12.3 to 0.89±23 ($p=.002$) and 0.69±16.4 ($p=.003$)
Reekers *et al.* (2016)[32]	To report on the first clinical experience with PA of the foot in patients with chronic critical limb ischaemia	In the majority of patients (n=59/68), PA showed an increase in volume flow, both increase in area under the curve (48%) and maximum peak density (21%)	No follow up	No reference standard	No clinical outcomes reported
Contrast enhanced ultrasound (CEUS)					
Duerschmied *et al.* (2010)[36]	To test whether the quantification of muscle perfusion of the lower limb by CEUS detects the success of revascularisation and whether it performs equally well in doing so as standard tests	PTA group: median TTP was 45 s (range 17 −73 s) before and 24 s (12−82 s) after intervention ($p=.015$). At follow up, median TTP was 22 s (16−63 s). Bypass group: median TTP decreased from 30 s (17−75 s) to 27 s (16−42 s; $p=.041$) directly, and to 21 s (12−30 s) 3−5 mo after surgery	3−5 mo	Compared with ABPI and PVR. Improvement in clinical stage (Fontaine)	Median ABPI improved significantly from 0.60 (0.0−1.08) to 0.85 (range 0.50 −1.47) ($p=.001$) and to 0.94 (0.56− 1.84) at follow up. Median amplitude reduction in PVR improved significantly from middle to none after PTA and from middle−high to none after bypass. Correlation between ABPI and TTP showed no significant difference after PTA or bypass
CT perfusion imaging					
Ma *et al.* (2021)[37]	To assess whether the regional evaluation of foot blood volume may guide direct revascularisation and if it will lead to better perfusion improvement than indirect revascularisation	Blood volume was significantly different from 48.95±33.36 mL/1 000 mL to 81.97±41.40 mL/1 000 mL ($p=.002$)	1 mo	Improvement in clinical stage (Rutherford classification)	Patients in the mild group had better pre-operative perfusion than the severe group: 58.20±33.24 *vs.* 30.45±26.28 mL/1 000 mL ($p=.039$). One month after treatment, there were no differences ($p=.28$)

Table 2-*continued*

Study (year)	Aim	Main outcomes	Follow up period	Diagnostic reference standard	Clinical outcomes
Indocyanine green (ICG) angiography (ICGA)					
Colvard *et al.* (2016)[39]	Prospectively determine the role of laser assisted fluorescence angiography in evaluating revascularisation outcomes for patients with PAD	Mean ingress, egress, and peak perfusion of the plantar side increased significantly from 7.1 to 12.4 units/s ($p<.001$), from 1.0 to 1.9 units/s ($p=.035$), and from 97.1 to 143.9 units ($p<.001$), respectively	Mean follow up time of 13.4 mo	Compared with ABPI. Improvement in walking distance and decrease in patient reported claudication symptoms	Patients with clinically successful outcomes showed significant improvements in ABPI, ingress, egress, and peak perfusion ($p<.001$, $p<.001$, $p=.044$, and $p<.001$, respectively). Overall change in ABPI significantly correlated with post-operative changes in ingress ($r=.33$; $p=.006$) and peak perfusion ($r=.24$; $p=.049$)
Mironov *et al.* (2019)[44]	To determine the predictive value of intraprocedural real time perfusion scanning on clinical outcome (limb salvage/wound healing) in patients with critical ischaemia	After successful angioplasty, 39% had an initial decrease in ingress rate and 57% had a decreased total inflow. Ingress of the whole foot increased from 118±83 to 125±85. Ingress rate of the whole foot from 17±19 to 20±20	6 mo	Compared with ABPI, Rutherford stage and wound healing/ formation according to TIME classification	No significant correlation between ABPI and baseline perfusion parameters. Inflow perfusion rate correlated significantly with Rutherford stage (Spearman rho=.398, $p=.036$). None of the perfusion variables was a significant predictor of wound healing
Patel *et al.* (2018)[40]	To assess ICGA data before and after revascularisation to demonstrate the successes of revascularisation procedure in CLI patients	In patients with a healed ulcer: maximum unit increased significantly from 22.84±33.43 to 63.43±46.66 ($p<.001$). Blush time decreased from 19.259±14.833 to 18.157±11.466 ($p=.65$). Blush rate increased from 2.287±4.747 to 7.144±13.1788 ($p=.008$)	Mean follow up time was 82.1±60.5 d	Compared with ABPI and $TcPO_2$	ABPI increased from 0.35±0.24 to 0.83±0.40 ($p<.001$). $TcPO_2$ increased from 30.92±18.69 to 48.57±20.46 ($p<.001$). The ABPI showed a correlation with maximum unit ($r=-.031$, $p=.86$), blush time ($r=.135$; $p=.44$), and blush rate ($r=.067$, $p=.69$). $TcPO_2$ showed a correlation with maximum unit ($r=.01$, $p=.69$), blush time ($r=.21$, $p=.08$), and blush rate ($r=-.08$, $p=.63$)
Rother *et al.* (2017)[42]	To establish IFA in the context of tibial bypass surgery and to gain information about the influence of macroscopic revascularisation on the level of microcirculation	Cumulated IN of the plantar and dorsal side of the foot showed significant increase from 96.0 (range 200) to 127.0 (range 227.0) ($p<.001$) in brightest stats and 38.0 (range 137.0) to 42.0 (range 149.0) ($p=.030$) in background stats. Cumulated InR showed significant increase from 3.6 (range 19.9) to 10.9 (range 42.7) ($p<.001$) in brightest stats and 0.8 (range 7.6) to 1.6 (range 10.7) ($p<.001$) in background stats	Mean follow up time was 8.28±4.46 mo	Compared with ABPI. Wound sizes were reported	ABPI showed a significant improvement from 0.42±0.260 to 0.91±0.220 ($p<.001$). The cumulated ingress and ingress rate correlated significantly positive with the ABPI; IN, $p=.009$; InR, $p=.005$ in background stats and IN, $p=.011$; InR, $p=.014$ in brightest stats
Rother *et al.* (2018)[43]	To employ ICGA to investigate the actual perfusion in both direct and indirectly revascularised angiosomes after tibial bypass surgery	The ingress of the plantar side showed improvement from 115.00 (5.00−200.00) to 135.00 (35.00−240.00) ($p=.009$) and the ingress rate from 5.80 (0.20− 20.00) to 11.40 (0.50− 35.70) ($p=.001$). The ingress of the dorsal side showed improvement from 86.00 (0.00− 218.00) to 145.00 (23.00−250.00) ($p<.001$) and the ingress rate from 3.30 (0.00 −18.60) to 10.00 (0.30−24.60) ($p<.001$).	Median follow up was 11 mo (range 4−18 mo)	Compared with ABPI and duplex ultrasound. Wound status was recorded	ABPI showed a significant improvement from 0.40 (range 0.00−0.93) to 0.91 (range 0.33−1.29) ($p<.001$). Median wound healing time was 4.25 mo
Settembre *et al.* (2017)[45]	To study the usefulness of ICG imaging in the immediate quality control of revascularisation and the sensitivity of the technique to distinguish early failures in the revascularisation	Mean ingress increased from 81±47 units to 120±5 units; mean ingress rate values were 4.2±4.9 units/s and 8.0±6.2 units/s ($p=.001$)	No follow up	Compared with ABPI and TBI values	Mean ABPI increased from 0.41±0.14 to 0.85±0.2 ($p<.001$), and TBI increased from 29±12 to 49±20 ($p=.07$)

All values are given as mean ± standard deviation or as median (interquartile range). LSFG = laser speckle flowgraphy; PAD = peripheral arterial disease; BSSP = beat strength of skin perfusion; MRI = magnetic resonance imaging; IC = intermittent claudication; PTA = percutaneous transluminal angioplasty; IA = iliac artery; SFA = superficial femoral artery; ASL = arterial spin labelling; TTP = time to peak; ABPI = ankle brachial pressure index; sO_2 = oxygen saturation; AU = arbitrary unit; StO_2 = tissue oxygen saturation; TBI = toe brachial index; CLI = critical limb ischaemia; rsO_2 = regional tissue oxygen saturation; SpO_2 = peripheral capillary oxygen saturation; EVT = endovascular therapy; CI = confidence interval; 2D = two dimensional; BTK = below the knee; ATA = anterior tibial artery; ROI = region of interest; PD = peak density; AUC = area under the curve; AT = arrival time; LTT = leg transit time; MTT = mean transit time; PDV = peak density value; TAC = time attenuation curve; WI = wash in; PA = perfusion angiography; PVR = pulse volume recording; CT = computed tomography; TIME = tissue, infection or inflammation, moisture imbalance, and edge of wound; $TcPO_2$ = transcutaneous oxygen pressure; IFA = intra-operative fluorescence angiography; IN = ingress; InR = ingress rate; CEUS = contrast enhanced ultrasound; I = Intensity; ICG = indocyanine green; ICGA = indocyanine green angiography; NIRS = near infrared spectroscopy; SPP = skin perfusion pressure.

Table 3. Advantages and disadvantages of all included peri-procedural tissue perfusion techniques for patients with peripheral arterial disease of the lower limbs

Technique	Advantages	Disadvantages
LSCI	Short measuring times[10] Acquisition of time dependent blood flow images[10]	Low penetration depth of 0.1−0.5 mm[13,47] Sensitivity for motion artefacts, temperature changes, and different medication[13,47]
MRIp	Quantitative perfusion values can be obtained with low signal to noise ratio[14] No need for an exogenous contrast agent[14]	Underestimation of peripheral blood flow[14] Claustrophobia[14] High costs[14]
O_2C	Quick and in real time[47]	Measurements are restricted to a small tissue volume[47] Penetration depth cannot be exactly determined, so the actual measurement spot stays unclear[48]
NIRS	Applicability at most locations on the lower extremity without interfering with the intervention[19]	Real time haemodynamic changes are difficult to obtain due to patient movement[19]
PT	Cost effectiveness[22] Non-contacting technique[22] Able to produce multiple recordings at short time intervals[22] Both limbs can be assessed within one test[22]	Toe skin temperatures are known to be significantly affected by ambient temperatures[22]
SPP	Quick technique[10] It can be applied on several spots on the lower extremity[10]	Cuff inflation can be painful in patients with tissue loss or infected wounds[10] Limited by motion artefacts[49]
2D-PA	The use of standard DSA runs so no extra ionising radiation or contrast agents are needed[32]	Heterogeneity in DSA acquisition protocols[32] Impairing motion artefacts in up to 10% of the patients[32]
CEUS	Real time visualisation of perfusion in the skeletal muscles[13] Easily accessible[13]	Operator dependency[13] Sensitivity for motion and bone artefacts[13]
CT-PI	Feasibility[37] Reproducibility[37] Excellent intra-observer and interobserver agreement[37]	Impairing motion artefacts and foot deformation between pre-revascularisation and post-revascularisation images[37] The use of ionising radiation[37] High cost[37]
ICGA	ICG is a water soluble, non-radioactive, non-ionising, and non-toxic contrast agent[40]	Low penetration depth[13] Expensive imaging systems[13] Measurements affected by temperature and medication (vasoactive substances) [13] The need for intravenous contrast administration[13]

LSCI = laser speckle contrast imaging; MRIp = magnetic resonance imaging perfusion; O_2C = micro-lightguide spectrophotometry; NIRS = near infrared spectroscopy; PT = plantar thermography; SPP = skin perfusion pressure; DSA = digital subtraction angiography; 2D-PA = two dimensional perfusion angiography; CEUS = contrast enhanced ultrasound; CT-PI = computed tomography perfusion imaging; ICGA = indocyanine green (ICG) angiography.

Contrast enhanced ultrasound. CEUS uses an intravenous injection of microbubbles combined with ultrasound, which allows for analysis of the intravascular distribution of this hyperechogenic contrast agent over time.[35] CEUS can be performed with a penetration depth of 4 - 15 cm.[35,36] Quantitative measurements are performed by determining the TTP contrast intensity.[36]

Computed tomography perfusion imaging. CT perfusion imaging uses a flat panel detector angiographic system to capture real time parenchymal blood volume, using an automated intra-arterial injection of an iodine based contrast agent.[37] Imaging of the entire foot and ankle can be performed. Post-processing software is used for three dimensional reconstruction and conversion to colour coded perfusion maps.

Indocyanine green angiography. ICGa uses a laser light source, in the near infrared light spectrum (650 − 900 nm), combined with intravenous injection of ICG.[13,38] A charged coupled device camera captures a real time image.[39,40] ICGa provides approximately 3 − 7 mm of tissue penetration,[41−43] and could therefore be used as an indicator of superficial tissue perfusion.[41] Dedicated software can be used to analyse quantitatively ICG intensity in the entire image or in a chosen ROI.[39,40,42−45]

Study outcomes

Six studies including 335 patients, ranging from 30 to 101 patients with Fontaine IIb − IV PAD, were found. A significant improvement in perfusion directly after revascularisation, by means of multiple ICGa perfusion parameters, was found.[39,40,42−45] All studies measured ABPI and showed significant improvement after revascularisation. Colvard *et al.*,[39] Patel *et al.*,[40] and Rother *et al.*[42] showed a correlation of different ICGa perfusion parameters with an overall change in ABPI. Mironov *et al.* showed that none of the perfusion variables was a significant predictor of wound healing.[44] However, the studies

Table 4. Bias and quality assessment of the 26 included studies on peri-procedural tissue perfusion techniques for patients with lower limb peripheral arterial disease according to QUADAS-2

Study (year)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Kikuchi *et al.* (2019)[10]	High	Unclear	Unclear	Unclear	Low	Low	Unclear
Grözinger *et al.* (2014)[12]	Unclear	High	Unclear	Low	Low	Low	Low
Rother *et al.* (2017)[16]	Low	High	Low	Low	Low	Low	Low
Boezeman *et al.* (2016)[19]	Low	High	Low	Low	Low	Low	Low
Kundra *et al.* (2020)[21]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Chang *et al.* (2020)[22]	Low	Low	Low	Low	Low	Low	Low
Ichihashi *et al.* (2020)[27]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Ikeoka *et al.* (2018)[25]	High	Unclear	Unclear	Low	Low	Low	Unclear
Ikeoka *et al.* (2020)[9]	High	Unclear	Unclear	Low	Low	Low	Low
Kawarada *et al.* (2014)[24]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Mochizuki *et al.* (2016)[23]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Hinrichs *et al.* (2017)[28]	High	Low	Low	Low	Low	Low	Low
Jens *et al.* (2015)[30]	Low	Unclear	Unclear	Unclear	High	Low	Unclear
Kim *et al.* (2017)[34]	Unclear	High	Low	Low	Low	Low	Low
Murray *et al.* (2016)[29]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Ng *et al.* (2019)[31]	Low	High	Low	Unclear	Low	Low	Low
Pärsson *et al.* (2020)[33]	Unclear	Unclear	Unclear	Low	Low	Low	Low
Reekers *et al.* (2016)[32]	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Duerschmied *et al.* (2010)[36]	High	High	Unclear	Unclear	Low	Low	Low
Ma *et al.* (2021)[37]	Low	Unclear	Unclear	Low	Low	Low	Low
Colvard *et al.* (2016)[39]	High	Unclear	Unclear	Unclear	Low	Low	Low
Mironov *et al.* (2019)[44]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Patel *et al.* (2018)[40]	Unclear	Unclear	Unclear	Low	Low	Low	Low
Rother *et al.* (2017)[42]	Low	High	Unclear	Low	Low	Low	Low
Rother *et al.* (2018)[43]	Low	High	Low	Low	Low	Low	Low
Settembre *et al.* (2017)[45]	Unclear	High	Unclear	Unclear	Low	Low	Low

were difficult to compare owing to heterogeneity in imaging devices and protocols.

DISCUSSION

In this systematic review, 10 techniques were found that assessed tissue perfusion in patients suffering Fontaine II — IV PAD before and within 24 hours after revascularisation procedures. Twenty-three of the 26 included studies had a small sample size ($n < 50$) and only investigated the feasibility of determining the change in tissue perfusion with these techniques. No diagnostic accuracy or correlation with treatment outcomes, such as wound infection and healing, amputation rate, need for re-admission, quality of life or mobility, were demonstrated.[46] The results of the 26 eligible studies, which were mostly of poor quality according to the QUADAS-2 tool, were not sufficient to substantiate implementation in daily clinical practice yet. Comparing and pooling of data and results was not

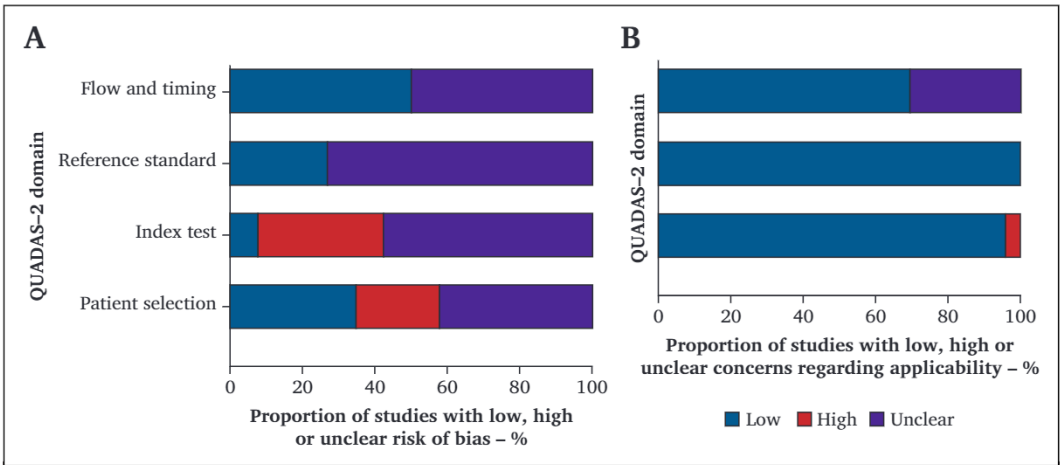

Figure 2. Graphical display of bias and quality assessment according to QUADAS-2 tool of studies on peri-procedural tissue perfusion techniques for patients with peripheral arterial disease of the lower limbs.

meaningful because of the limited number of studies per technique. Besides, heterogeneity in inclusion criteria, patient selection, measurement protocols, follow up time, measurement of clinical outcomes, and clinical endpoints made pooling impossible. Normally, the QUADAS-2 tool is used to assess studies evaluating diagnostic tests that compare the diagnostic accuracy of the index test *vs.* a reference standard test. Six of the included studies in this review did not describe a reference standard and the remaining studies showed high heterogeneity within described reference standards: ABPI; TBI; clinical classifications; wound healing; or amputation rate. This is an important limitation of the included studies; however, considering available quality assessment tools, there was no reasonable alternative to the QUADAS-2 tool.

Before assessment of the microcirculation can be implemented as standard care, multiple issues have to be resolved. Measurement protocols need to be optimised and standardised; techniques should be validated in large clinical cohorts; reliability assessments should be performed; and cutoff values need to be determined with a high sensitivity and specificity. To do so, a well defined study population of patients with Fontaine III — IV PAD should be included and analysed on major clinical outcomes such as the aforementioned wound infection and healing, amputation rate, need for re-admission, quality of life, and mobility.[46]

One of the main reasons to perform endovascular or open revascularisation procedures in patients suffering from PAD is to improve tissue perfusion and skin oxygenation of the lower leg and foot. This is of the utmost importance in patients with ischaemic ulcers, to facilitate healing. Ideally, the increase in perfusion and oxygenation of the diseased tissue can be monitored in real time during an intervention. Endovascular revascularisation is currently considered successful when an arterial stenosis or occlusion is overcome and no haemodynamically significant lesion is left behind. Outcomes are therefore focused on anatomical results and thus the macrovasculature. It may be argued that as long as the tissue oxygenation and perfusion parameters in the lower leg and/or foot do not increase the intervention may be considered as not successful. Real time monitoring of these parameters may guide the vascular surgeon or interventionalist during the procedure to extend it (if possible) and to revascularise more feeding arteries. So far, none of the described techniques seem capable of doing this. Future studies should focus on this, and also try to associate the peri-procedural findings of changes in tissue perfusion and skin oxygenation with clinical outcomes including improvement in walking distance, pain relief, and time to wound healing. To do so, the first step would be to define validated normal values for the tissue perfusion techniques. It would be of great help if the course of tissue perfusion and skin oxygenation levels could be monitored in the early post-intervention period. It may be argued that tissue perfusion takes some time after revascularisation to set a new equilibrium. So far, it is unknown when this new equilibrium is reached. Repeated measurements in the early post-intervention period, even at home, may be helpful in determining a decrease that may be associated with early treatment failures and the need to perform additional Doppler ultrasound, CT angiography, or magnetic resonance angiography, and eventually early re-intervention. Finally, the cost of equipment was not studied. Equipment cost was difficult to determine because its place in the clinic has not yet crystallised and the reimbursement systems are country and sometimes even hospital dependent.

CONCLUSION

This systematic review provides an overview of 10 tissue perfusion techniques used before and within 24 hours after revascularisation procedures of the lower extremity to treat PAD. Within the broad inclusion criteria, only 26 articles were found to be eligible for inclusion in this review. Ideally, a tissue perfusion technique should guide the vascular surgeon or interventionalist in real time throughout the entire revascularisation procedure and be related to major clinical outcomes such as improvement in Fontaine classification and time to wound healing. The technique should be non-invasive, non-operator dependent, accurate, cost effective, and fast. At this time, evidence remains low regarding the diagnostic accuracy of these techniques. It is too early to recommend one of the currently available techniques as a decision tool in the treatment of patients with PAD. Prospective observational studies, to relate peri-interventional assessments with clinical outcomes after a certain length of follow up, are necessary as a first step in the implementation of one of these techniques into daily vascular practice.

CONFLICTS OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.08.017.

REFERENCES

1 Becker F, Robert-Ebadi H, Ricco J-B, Setacci C, Cao P, de Donato G, et al. Chapter I: Definitions, epidemiology, clinical presentation and prognosis. *Eur J Vasc Endovasc Surg* 2011;**42**(Suppl. 2):S4—12.

2 Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg* 2019;**58**(1S):S1—S109.

3 Mizzi A, Cassar K, Bowen C, Formosa C. The progression rate of peripheral arterial disease in patients with intermittent claudication: a systematic review. *J Foot Ankle Res* 2019;**12**:40.

4 Schreuder SM, Hendrix YMGA, Reekers JA, Bipat S. Predictive parameters for clinical outcome in patients with critical limb ischemia who underwent percutaneous transluminal angioplasty (PTA): a systematic review. *Cardiovasc Intervent Radiol* 2018;**41**:1—20.

5 Reed GW, Raeisi-Giglou P, Kafa R, Malik U, Salehi N, Shishehbor MH. Hospital readmissions following endovascular therapy for critical limb ischemia: associations with wound healing, major adverse limb events, and mortality. *J Am Heart Assoc* 2016;**5**:e003168.
6 Pennell DJ. Editorial: To BOLDly go where positron emission tomography has been before. *Circ Cardiovasc Imaging* 2010;**3**:2–4.
7 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preffered reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;**4**:1.
8 Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529.
9 Ikeoka K, Watanabe T, Shinoda Y, Minamisaka T, Fukuoka H, Inui H, et al. Below-the-ankle arrival time as a novel limb tissue perfusion index: two-dimensional perfusion angiography evaluation. *J Endovasc Ther* 2020;**27**:198–204.
10 Kikuchi S, Miyake K, Tada Y, Uchida D, Koya A, Saito Y, et al. Laser speckle flowgraphy can also be used to show dynamic changes in the blood flow of the skin of the foot after surgical revascularization. *Vascular* 2019;**27**:242–51.
11 Draijer M, Hondebrink E, Leeuwen T Van, Steenbergen W. Review of laser speckle contrast techniques for visualizing tissue perfusion. *Lasers Med Sci* 2009;**24**:639–51.
12 Grözinger G, Pohmann R, Schick F, Grosse U, Syha R, Brechtel K, et al. Perfusion measurements of the calf in patients with peripheral arterial occlusive disease before and after percutaneous transluminal angioplasty using mr arterial spin labeling. *J Magn Reson Imaging* 2014;**40**:980–7.
13 Bajwa A, Wesolowski R, Patel A, Saha P, Ludwinski F, Smith A, et al. Assessment of tissue perfusion in the lower limb current methods and techniques under development. *Circ Cardiovasc Imaging* 2014;**7**:836–43.
14 Ma KF, Kleiss SF, Schuurmann RCL, Bokkers RPH, Ünlü Ç, De Vries JPPM. A systematic review of diagnostic techniques to determine tissue perfusion in patients with peripheral arterial disease. *Expert Rev Med Devices* 2019;**16**:697–710.
15 Englund EK, Langham MC. Quantitative and dynamic MRI measures of peripheral vascular function. *Front Physiol* 2020;**11**:120.
16 Rother U, Krenz K, Lang W, Horch RE, Schmid A, Heinz M, et al. Immediate changes of angiosome perfusion during tibial angioplasty. *J Vasc Surg* 2017;**65**:422–30.
17 Gyldenlove T, Jorgensen LP, Schroeder TV. Micro-lightguide spectrophotometry (O2C) for lower limb perfusion: effects of exercise walking in claudicants. *Int J Angiol* 2019;**28**:161–6.
18 Mesquita RC, Putt M, Chandra M, Yu G, Xing X, Han SW, et al. Diffuse optical characterization of an exercising patient group with peripheral artery disease. *J Biomed Opt* 2013;**18**:057007.
19 Boezeman RPE, Becx BP, van den Heuvel DAF, Unlu C, Vos JA, de Vries JPPM. Monitoring of foot oxygenation with near-infrared spectroscopy in patients with critical limb ischemia undergoing percutaneous transluminal angioplasty: a pilot study. *Eur J Vasc Endovasc Surg* 2016;**52**:650–6.
20 Patel HJ. Near infrared spectroscopy: basic principles and use in tablet evaluation. *Int J Chem Life Sci* 2017;**6**:2006.
21 Kundra TS, Thimmarayappa A, Subash SS, Kaur P. Monitoring of limb perfusion after vascular surgery in critical limb ischemia using near-infrared spectroscopy: a prospective observational study. *Ann Card Anaesth* 2020;**23**:429–32.
22 Chang WC, Wang CY, Cheng Y, Hung YP, Lin TH, Chen WJ, et al. Plantar thermography predicts freedom from major amputation after endovascular therapy in critical limb ischemic patients. *Medicine (Baltimore)* 2020;**99**:e22391.
23 Mochizuki Y, Hoshina K, Shigematsu K, Miyata T, Watanabe T. Distal bypass to a critically ischemic foot increases the skin perfusion pressure at the opposite site of the distal anastomosis. *Vascular* 2016;**24**:361–7.
24 Kawarada O, Yasuda S, Nishimura K, Sakamoto S, Noguchi M, Takahi Y, et al. Effect of single tibial artery revascularization on microcirculation in the setting of critical limb ischemia. *Circ Cardiovasc Interv* 2014;**7**:684–91.
25 Ikeoka K, Hoshida S, Watanabe T, Shinoda Y, Minamisaka T, Fukuoka H, et al. Pathophysiological significance of velocity-based microvascular resistance at maximal hyperemia in peripheral artery disease. *J Atheroscler Thromb* 2018;**25**:1128–36.
26 Pan X, Chen G, Wu P, Han C, Ho JK. Skin perfusion pressure as a predictor of ischemic wound healing potential. *Biomed Rep* 2018;**8**:330–4.
27 Ichihashi S, Takahara M, Fujimura N, Shibata T, Fujii M, Kato T, et al. Changes in skin perfusion pressure after endovascular treatment for chronic limb-threatening ischemia. *J Endovasc Ther* 2020;**28**:208–14.
28 Hinrichs JB, Murray T, Akin M, Lee M, Brehm MU, Wilhelmi M, et al. Evaluation of a novel 2D perfusion angiography technique independent of pump injections for assessment of interventional treatment of peripheral vascular disease. *Int J Cardiovasc Imaging* 2017;**33**:295–301.
29 Murray T, Rodt T, Lee MJ. Two-dimensional perfusion angiography of the foot: technical considerations and initial analysis. *J Endovasc Ther* 2016;**23**:58–64.
30 Jens S, Marquering HA, Koelemay MJW, Reekers JA. Perfusion angiography of the foot in patients with critical limb ischemia: description of the technique. *Cardiovasc Intervent Radiol* 2015;**38**:201–5.
31 Ng JJ, Papadimas E, Dharmaraj RB. Assessment of Flow after lower extremity endovascular revascularisation: a feasibility study using time attenuation curve analysis of digital subtraction angiography. *EJVES Short Rep* 2019;**45**:1–6.
32 Reekers JA, Koelemay MJW, Marquering HA, van Bavel ET. Functional imaging of the foot with perfusion angiography in critical limb ischemia. *Cardiovasc Intervent Radiol* 2016;**39**:183–9.
33 Pärsson HN, Lundin N, Lindgren H. 2D perfusion-angiography during endovascular intervention for critical limb threatening ischemia – a feasibility study. *JRSM Cardiovasc Dis* 2020;**9**. 204800402091539.
34 Kim AH, Shevitz AJ, Morrow KL, Kendrick DE, Harth K, Baele H, et al. Characterizing tissue perfusion after lower extremity intervention using two-dimensional color-coded digital subtraction angiography. *J Vasc Surg* 2017;**66**:1464–72.
35 Dietrich CF, Averkiou M, Nielsen MB, Barr RG, Burns PN, Calliada F, et al. How to perform Contrast-enhanced ultrasound (CEUS). *Ultrasound Int Open* 2018;**4**:E2–15.
36 Duerschmied D, Maletzki P, Freund G, Olschewski M, Bode C, Hehrlein C. Success of arterial revascularization determined by contrast ultrasound muscle perfusion imaging. *J Vasc Surg* 2010;**52**:1531–6.
37 Ma J, Lai Z, Shao J, Lei J, Li K, Wang J, et al. Infrapopliteal endovascular intervention and the angiosome concept: intraoperative real-time assessment of foot regions' blood volume guides and improves direct revascularization. *Eur Radiol* 2021;**31**:2144–52.
38 Yuan B, Chen N, Zhu Q. Emission and absorption properties of indocyanine green in Intralipid solution. *J Biomed Opt* 2004;**9**:497.
39 Colvard B, Itoga NK, Hitchner E, Sun Q, Long B, Lee G, et al. SPY technology as an adjunctive measure for lower extremity perfusion. *J Vasc Surg* 2016;**64**:195–201.
40 Patel HM, Bulsara SS, Banerjee S, Sahu T, Sheorain VK, Grover T, et al. Indocyanine green angiography to prognosticate healing of foot ulcer in critical limb ischemia: a novel technique. *Ann Vasc Surg* 2018;**51**:86–94.
41 Zimmermann A, Roenneberg C, Reeps C, Wendorff H, Holzbach T, Eckstein HH. The determination of tissue perfusion and collateralization in peripheral arterial disease with indocyanine green fluorescence angiography. *Clin Hemorheol Microcirc* 2012;**50**:157–66.

42 Rother U, Lang W, Horch RE, Ludolph I, Meyer A, Regus S. Microcirculation evaluated by intraoperative fluorescence angiography after tibial bypass surgery. *Ann Vasc Surg* 2017;**40**:190–7.
43 Rother U, Lang W, Horch RE, Ludolph I, Meyer A, Gefeller O, et al. Pilot assessment of the angiosome concept by intra-operative fluorescence angiography after tibial bypass surgery. *Eur J Vasc Endovasc Surg* 2018;**55**:215–21.
44 Mironov O, Zener R, Eisenberg N, Tan KT, Roche-Nagle G. Real-time quantitative measurements of foot perfusion in patients with critical limb ischemia. *Vasc Endovasc Surg* 2019;**53**:310–5.
45 Settembre N, Kauhanen P, Alback A, Spillerova K, Venermo M. Quality control of the foot revascularization using indocyanine green fluorescence imaging. *World J Surg* 2017;**41**:1919–26.
46 Ambler GK, Brookes-Howell L, Jones JAR, Verma N, Bosanquet DC, Thomas-Jones E, et al. Development of core outcome sets for people undergoing major lower limb amputation for complications of peripheral vascular disease. *Eur J Vasc Endovasc Surg* 2020;**60**:730–8.
47 Mennes OA, van Netten JJ, Slart RHJ, Steenbergen W. Novel optical techniques for imaging microcirculation in the diabetic foot. *Curr Pharm Des* 2018;**24**:1304–16.
48 Marcoccia A, Klein-Weigel PF, Gschwandtner ME, Wautrecht JC, Matuska J, Rother U, et al. Microcirculatory assessment of vascular diseases. *Vasa* 2020;**49**:175–86.
49 Misra S, Shishehbor MH, Takahashi EA, Aronow HD, Brewster LP, Bunte MC, et al. Perfusion assessment in critical limb ischemia: principles for understanding and the development of evidence and evaluation of devices: a scientific statement from the American Heart Association. *Circulation* 2019;**140**:e657–72.