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 Moumnie, Jean-Paul P.M. de Vries e; 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 December 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.
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.\(^4\) Clinical outcomes after a revascularisation procedure remain unpredictable when current imaging techniques are used.\(^5\) 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 (O₂C), 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. 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, 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, creating an interference pattern called a speckle pattern. 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.

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. By subtracting tagged images from a control image, a perfusion signal is obtained. Regions of interest (ROIs) are drawn in muscle groups, from where a perfusion time course is extracted. Thereafter, parameters of interest can be extracted. 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.

Micro-lightguide spectrophotometry. O2C, or “oxygen to see”, uses a combination of laser Doppler flowmetry and spectroscopy. O2C is determined using white light and laser light, with a penetration depth up to 2 mm reaching the dermis. 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 (sO2); relative haemoglobin (rHB) amount; relative blood flow; and blood flow velocity.

Near-infrared spectroscopy. NIRS measures single tissue oxygen saturation, continuously, with a maximum imaging depth of approximately 15—20 mm, including muscle tissue. 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. 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.](https://example.com/flow_diagram.png)
**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. (2020) | Prospective multicentre cohort study | 147/147 (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)  | Prospective cohort study          | 33/33 (7 lb, 13 III and 14 IV)  | Before and the day after revascularisation                 | Dorsal and plantar side of the foot                                                   | SensiLase PAD 3000 (Vasamed; Eden Prairie, MN, USA)                                  |
| Ikeoka et al. (2020)  | Prospective cohort study          | 33/33 (7 lb, 13 III and 14 IV)  | Before and the day after revascularisation                 | Dorsal and plantar side of the foot                                                   | SensiLase PAD 3000 (Vasamed; Eden Prairie, MN, USA)                                  |
| Kawarada et al. (2020) | Retrospective study               | 44/44 (57 lb)                   | Before and one day after revascularisation                 | Dorsal and plantar side of the foot                                                   | SensiLase PAD 3000 (Vasamed; Eden Prairie, MN, USA)                                  |
| Kikuchi et al. (2019) | Prospective cohort study          | 31/33 (7 lb, 4 III, 22 IV)      | Before and immediately, three, and seven days after      | Plantar side of the foot, lateral and medial sides                                   | Laser doppler probe (Philips, Amsterdam, Netherlands)                                |
| Mochizuki et al. (2016) | Retrospective study               | 44/44 (57 lb, 4 III, 22 IV)    | Before and after revascularisation                        | Dorsal and plantar side of the foot, ankle, below and above knee                      | LASER Doppler PV 2000 (Vasamedics, St. Paul, MN, USA)                                 |
| **Micro-lightguide spectrophotometry (O2C)** |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Gratzinger et al. (2014) | Prospective cohort study          | 10/10 (1 lb, 9 lb)              | Before and after revascularisation                        | Soleus and tibialis anterior muscle during reactive hyperaemia                       | 3 Tesla system (Magnetom Trio; Siemens Healthcare, Erlangen, Germany)                |
| **MRI perfusion**     |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Rother et al. (2017)  | Prospective cohort study          | 30/30 (8 III, 22 IV)            | Continuously during endovascular revascularisation       | Dorsal and plantar side of the foot, lateral side of the ankle. Control probe on the   | The O₂C (LEA Medizintechnik, Giesen, Germany)                                        |
| **Near infrared spectroscopy** |                              |                                 |                                                             |                                                                                      |                                                                                      |
| Boezeman et al. (2016) | Prospective cohort study          | 14/14 (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 NR8-200 system (Hamamatsu Photonics K.K, Hamamatsu, Japan)                |
| **Plantar thermography** |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Kundra et al. (2020)  | Prospective cohort study          | 30/30 (Unknown)                 | Continuously during endovascular revascularisation until 12 h after the procedure | The operative limb                                                                     | Not reported                                                                         |
| **Skin perfusion pressure** |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Ichihashi et al. (2020) | Prospective multicentre cohort study | 147/147 (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)  | Prospective cohort study          | 16/16 (14 lb, 2 III)            | Before and after revascularisation                        | Dorsal and plantar side of the foot                                                   | SSP (Nabri MV monitor; Nexis, Tokyo, Japan)                                           |
| Ikeoka et al. (2020)  | Prospective cohort study          | 33/33 (7 lb, 13 III and 14 IV)  | Before and the day after revascularisation                 | Dorsal and plantar side of the foot                                                   | SensiLase PAD 3000 (Vasamed; Eden Prairie, MN, USA)                                  |
| Kawarada et al. (2020) | Retrospective study               | 44/44 (57 lb)                   | Before and one day after revascularisation                 | Dorsal and plantar side of the foot                                                   | SensiLase PAD 3000 (Vasamed; Eden Prairie, MN, USA)                                  |
| Kikuchi et al. (2019) | Prospective cohort study          | 31/33 (7 lb, 4 III, 22 IV)      | Before and immediately, three, and seven days after      | Plantar side of the foot, lateral and medial sides                                   | Laser doppler probe (Philips, Amsterdam, Netherlands)                                |
| Mochizuki et al. (2016) | Retrospective study               | 44/44 (57 lb, 4 III, 22 IV)    | Before and after revascularisation                        | Dorsal and plantar side of the foot, ankle, below and above knee                      | LASER Doppler PV 2000 (Vasamedics, St. Paul, MN, USA)                                 |
| **2D perfusion angiography** |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Hirths et al. (2017)  | Retrospective study               | 21/21 (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)  | Prospective cohort study          | 33/33 (7 lb, 13 III and 14 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)    | Prospective cohort study          | 18/18 (III or IV, exact numbers unknown) | At the start and end of the endovascular procedure | ROI included the region between the tibial joint and the mid-metatarsal region        | Allura XperF20 system with post-processing software, Interventional Workstation R1.1 with 2D perfusion R1 (Philips Healthcare) |
| Kim et al. (2017)     | Prospective cohort study          | 16/16 (4 lb, 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 | Allura XperF20 system and postprocessing software from Philips (Interventional Workstation R1.0.1; Philips Healthcare) |
| Murray et al. (2016)  | Retrospective study               | 21/21 (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 XperF20 system and postprocessing software from Philips (Interventional Workstation R1.0.1; Philips Healthcare) |
| Ng et al. (2019)      | Retrospective study               | 47/47 (8 III, 39 IV)            | At the start and end of the endovascular procedure        | ROI placed on the main runoff, of the ped vein of the foot                            | Artis zeevo and postprocessing software from Siemens (syngo iFlow; Siemens Healthcare) |
| Pirsan et al. (2020)  | Prospective cohort study          | 33/33 (11 III, 22 IV)           | At the start and end of the endovascular procedure        | ROI was manually placed between the tibial joint and the midtarsal region including part of the calcaneus | Allura XperF20 system with post-processing software (Interventional Workstation R1.0.1; Philips Healthcare) |
| Reekers et al. (2016) | Prospective cohort study          | 68/68 (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 XperF20 system with post-processing software (Interventional Workstation R1.1 with 2D perfusion R1; Philips Healthcare) |
| **Contrast enhanced ultrasound** |                                  |                                 |                                                             |                                                                                      |                                                                                      |
| Duerschiedt et al. (2010) | Prospective cohort study          | 34/34 (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, Milwaukie, WI, USA) |

Please cite this article as: Wermelink B et al., A Systematic Review and Critical Appraisal of Per-Procedural Tissue Perfusion Techniques and their Clinical Value in Patients with Peripheral Arterial Disease, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.017
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.\textsuperscript{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.\textsuperscript{19} ABPI or TBI showed a significant improvement after four weeks; however, no correlation with single tissue oxygen saturation directly after revascularisation was determined.\textsuperscript{19} The study by Kundra et al. showed a significant improvement in single tissue oxygen saturation after surgery, which correlated with Doppler signals.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9,10,23—25,27} Ikeoka et al. also showed a significant improvement in ABPI and ankle pressure.\textsuperscript{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.\textsuperscript{23,24}

**Invasive techniques**

Two dimensional perfusion angiography. 2D-PA determines tissue perfusion based on digital subtraction angiography (DSA) images, acquired during endovascular treatment.\textsuperscript{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.\textsuperscript{31} From this TAC, a wide range of parameters such as arrival time, time to peak (TTP) and wash in rate can be extracted.\textsuperscript{9,28—34} Furthermore, ratios for outflow and inflow can be determined (i.e., TTP\textsubscript{outflow}/TTP\textsubscript{inflow}) to overcome potential limitations of standardised pump injection.\textsuperscript{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.\textsuperscript{9,28—34} Furthermore, correlations were found between the ABPI, TBI or SPP and 2D-PA parameters.\textsuperscript{9,28,34} Murray et al. were the only authors who correlated 2D-PA with improvement in Fontaine stage, which showed no significant association.\textsuperscript{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) | To evaluate whether the new LSFG technology can capture dynamic changes in foot blood flow following surgical revascularisation for PAD | BSPP 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 < 0.01) | 7 d | No reference standard | No clinical outcomes |
| **MRI perfusion** | | | | | |
| Grötzing et al. (2014) | 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 | Mean perfusion value increased from 74±5.2 to 129±8.0 (p = 0.086) in the soleus muscle and from 53±3.5 to 111±7.5 (p = 0.041) in the tibialis anterior. TTP decreased from 59±29 s to 41±14 s (p = 0.09) in the soleus muscle and from 61±24 s to 41±18 s (p = 0.045) 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 < 0.001) Pain free walking distance improved from 86:157 m to no limit in 8 patients; two patients reported a restriction (70 and 500 m, respectively) |
| **Micro-lightguide spectrophotometry** | | | | | |
| Kuther et al. (2017) | To obtain further information on microcirculation changes during tissue hypoperfusion, validate and evaluate the relevance of the angiome concept by means of microcirculation measurements during tissue intervention | Mean SO2 significant improvement from 45.73% (1.00–95.55%) to 62.39% (2.12–98.04%) (p < 0.001). Overall flow parameter increased significantly from 19.96 AU (0.00–231.9 AU) to 32.01 AU (0.34–224.87 AU) (p < 0.001) | 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 < 0.001) |
| **Near infrared spectroscopy (NIRS)** | | | | | |
| Boezeman et al. (2016) | 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 SO2 values and ABPI and TBI | Before revascularisation the mean SO2 of opt 1 and opt 2 were 51±11% and 57±7%, respectively, and converted to baseline values of 100%. After revascularisation mean SO2 of opt 1 and opt 2 were 100±4±11% (p = 0.80) and 101±8±2.3% (p = 0.61) | 4 weeks | Compared with ABPI and TBI values | Mean ABPI and TBI increased significantly after four weeks (p < 0.01). ABPI and TBI values did not significantly correlate with SO2 values of opt 1 (p = 0.55 and p = 0.75, respectively) |
| Kundra et al. (2020) | 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 reO2 and limb pO2, from 27.27±3.92 and 38.13±5.25 to 41.97±1.25 and 58.13±1.64 (p < 0.001) directly after a revascularisation procedure. There was a significant improvement of 6 and 12 h after treatment (p < 0.001 and p < 0.001, respectively) | 12 h | Compared with Doppler examination | No clinical outcomes |
| **Planar thermography** | | | | | |
| Chang et al. (2020) | To investigate whether angiome 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 foot was significantly higher in the healing group vs. the non-healing group: (30.78°C [range 28.94–32.38°C]) vs. 29.42°C [28.64–31.39°C], p = 0.015, and 32.34°C [30.48–33.23°C] vs. 30.96°C [28.74–32.48°C], p = 0.004, respectively | 18 mo | Wound healing and freedom from major amputation | No significant difference in the mean pre-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) | 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 < 0.001). | 1 mo | No reference standard | No clinical outcomes |
| Ikoska et al. (2018) | 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 = 0.033); plantar side from 72.2±15.4 to 76.3±14.4 mmHg (p = 0.54). The increment of dorsal SPP was significantly larger than that of plantar SPP after EVT (p < 0.001) | No follow up | No reference standard | No clinical outcomes |
| Ikoska et al. (2020) | To assess the relationship between 2D perfusion analysis and SPPs before and after EVT in patients with RTO occlusive disease | Dorsal SPP increased significantly from 41.0±18 mmHg to 52.2±20 mmHg (p < 0.001) and plantar SPPs were significantly elevated from 49.8±22 mmHg to 57.5±23 mmHg (p = 0.000) | 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 < 0.001). Mean systolic ankle pressure increased significantly from 120±24 mmHg to 137±24 mmHg (p < 0.025) |
| Kawarada et al. (2014) | 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 angiome 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 < 0.001). With PTA revascularisation, plantar SPP increased significantly from 29.3±9.8 to 43.5±15.9 mmHg (p < 0.001) | 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±21.3 (dorsal) and 42.6±19.1 (plantar) mmHg (not significantly different) |
| Kikuchi et al. (2019) | 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 < 0.01). | 7 d | No reference standard | No clinical outcomes |
| Study (year)                  | Aim                                                                 | Main outcomes                              | Follow up period | Diagnostic reference standard | Clinical outcomes |
|-----------------------------|----------------------------------------------------------------------|--------------------------------------------|------------------|-------------------------------|-------------------|
| Mochizuki et al. (2016)     | 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     | To assess a novel perfusion angiography technique, flow analysis based on two ROIs placed in the treated vessel in patients with PAD | The mean TTPINFLOW/TTPFLOW significantly decreased from 1.81±1.37 to 0.95±0.89 (52.8% p<.001), PDINFLOW/PFLOW (36%) significantly increased from 0.72±0.44 to 0.98±0.43 (p<.001). AUCOUTFLOW/AUCFLOW 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. (2015)        | 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 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 |
| Jen et al. (2015)           | 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)           | 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±3.35 s to 5.03±3.03 s (p=.003). Wash in rate increased significantly from 82.81 to 121.9 l/s (p=.004). Width, LTT, TTP, MIT 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, MITT) and the degree of change in the ABPI was not significant. No correlation analysis with clinical outcomes |
| Murray et al. (2016)        | 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 4.63±3.76 to 5.99±3.3877 (p=.03) and in the forehead from 5.56±3.78 to 7.37±0.6350 (p=.13). No significant change in TTP or PDV was detected following angioplasty | Short term, exact period not reported | Improvement in clinical stage | 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)            | 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 (T10%−T50%, T1%−T50%, T10%−T90%), Percentages of contrast decay at specified time intervals after peak (T10, T15, T30, T45), and T15 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=-.482) with improvement in ABPI or TBI. No correlation analysis with clinical outcomes |
| Parsons et al. (2020)       | 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) (p=.007) and mean TTP from 4.1 (2.5−4.2) to 3.1 (2.3−3.9) (p=.009) was observed 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)       | 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=59/60), 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) | 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 TBI showed no significant difference after PTA or bypass |
| CT perfusion imaging         | 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/1000 mL to 81.97±41.40 mL/1000 mL (p=.002) | 1 mo | Improvement in clinical stage (Rutherford classification) | Patients in the mild group had better preoperative perfusion than the severe group: 58.20±31.24 vs 20.40±28.28 mL/1000 mL (p=.039). One month after treatment, there were no differences (p=.28) |

**Continued**
### Table 2-continued

| Study (year) | Aim | Main outcomes | Follow up period | Diagnostic reference standard | Clinical outcomes |
|--------------|-----|---------------|------------------|-------------------------------|-------------------|
| **Indocyanine green (ICG) angiography (ICGA)** | | | | | |
| Colvart et al. (2016) | | | | | |
| 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 | Mean follow up time was 6 mo | Compared with ABPI. Improvement in walking distance and decrease in patient reported claudication symptoms | No significant correlation between ABPI and baseline perfusion parameters. Follow perfusion rate correlated significantly with Rutherford stage ( Spearman rho=−0.398, p=0.036). None of the perfusion variables was a significant predictor of wound healing |
| Mironov et al. (2019) | 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 increase significantly from 22.8±4.33±46.66 (p<0.001). Blush time decreased from 19.259±14.833 to 18.157±11.466 (p=0.65). Blush rate increased from 2.287±4.747 to 7.144±13.1788 (p=0.008) | | |
| Patel et al. (2018) | To employ ICGA to investigate the actual perfusion in both direct and indirectly revascularised angioses after tibial bypass surgery | 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<0.001) in brightest stats and 38.0 (range 137.0) to 42.0 (range 149.0) (p<0.001) in background stats. Cumulated IN showed significant increase from 3.6 (range 19.9) to 10.9 (range 42.7) (p<0.001) in brightest stats and 0.8 (range 7.6) to 1.6 (range 10.7) (p<0.001) in background stats | Mean follow up time was 8.28±4.46 mo | Compared with ABPI. Wound sizes were recorded | |
| Rother et al. (2017) | 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 | The ingress of the plantar side showed improvement from 115.00 (5.00–200.00) to 135.00 (35.00–240.00) (p<0.009) and the ingress rate from 5.80 (0.20–20.00) to 11.40 (0.50–35.70) (p<0.001). The ingress of the dorsal side showed improvement from 86.00 (0.00–218.00) to 145.00 (23.00–250.00) (p<0.001) and the ingress rate from 3.30 (0.00–18.60) to 10.00 (30.30–24.60) (p<0.001). | Median follow up was 11 mo (range 4–18 mo) | Compared with ABPI and duplex ultrasound. Wound status was recorded | |
| Rother et al. (2018) | | | | | |
| To evaluate 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±1.4 units/s and 8.0±1.2 units/s (p<0.001) | No follow up | Compared with ABPI and TBI | Mean ABPI increased from 0.41±0.14 to 0.85±0.2 (p<0.001), and TBI increased from 29±12 to 49±20 (p<0.07) | 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; S0 = oxygen saturation; AU = arbitrary unit; SO2 = tissue oxygen saturation; TBI = toe brachial index; CLI = critical limb ischaemia; rsO2 = regional tissue oxygen saturation; SpO2 = 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; TAG = 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; TePO2 = transcutaneous oxygen pressure; IFA = intra-operative fluorescence angiography; IN = ingress; IR = ingress rate; CEUS = contrast enhanced ultrasound; I = Intensity; ICG = indocyanine green; ICGA = indocyanine green angiography; NIRS = near infrared spectroscopy; SPP = skin perfusion pressure. |
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<sup>22</sup> Acquisition of time dependent blood flows<sup>10</sup> | Low penetration depth of 0.1–0.5 mm<sup>14,47</sup> Sensitivity for motion artefacts, temperature changes, and different medication<sup>15,47</sup> |
| MRlp | Quantitative perfusion values can be obtained with low signal to noise ratio<sup>14</sup> No need for an exogenous contrast agent<sup>14</sup> | Underestimation of peripheral blood flow<sup>14</sup> Claustrophobia<sup>14</sup> High costs<sup>49</sup> |
| O<sub>2</sub>C | Quick and in real time<sup>47</sup> | Measurements are restricted to a small tissue volume<sup>47</sup> Penetration depth cannot be exactly determined, so the actual measurement spot stays unclear<sup>48</sup> |
| NIRs | Applicability at most locations on the lower extremity without interfering with the intervention<sup>19</sup> | Real time haemodynamic changes are difficult to obtain due to patient movement<sup>19</sup> |
| PT | Cost effectiveness<sup>23</sup> Non-contacting technique<sup>22</sup> Able to produce multiple recordings at short time intervals<sup>25</sup> Both limbs can be assessed within one test<sup>22</sup> | Foot skin temperatures are known to be significantly affected by ambient temperatures<sup>13</sup> |
| SPP | Quick technique<sup>10</sup> It can be applied on several spots on the lower extremity<sup>14</sup> | Cuff inflation can be painful in patients with tissue loss or infected wounds<sup>15</sup> Limited by motion artefacts<sup>49</sup> |
| 2D-PA | The use of standard DSA runs so no extra ionising radiation or contrast agents are needed<sup>32</sup> | Heterogeneity in DSA acquisition protocols<sup>32</sup> Impairing motion artefacts in up to 10% of the patients<sup>32</sup> |
| CEUS | Real time visualisation of perfusion in the skeletal muscles<sup>13</sup> Easily accessible<sup>13</sup> | Operator dependency<sup>13</sup> Sensitivity for motion and bone artefacts<sup>13</sup> |
| CT-PI | Feasibility<sup>37</sup> Reproducibility<sup>37</sup> Excellent intra-observer and interobserver agreement<sup>27</sup> | Impairing motion artefacts and foot deformation between pre-revascularisation and post-revascularisation images<sup>7</sup> The use of ionising radiation<sup>7</sup> High cost<sup>7</sup> |
| ICGA | ICG is a water soluble, non-radioactive, non-ionsing, and non-toxic contrast agent<sup>19</sup> | Low penetration depth<sup>13</sup> Expensive imaging systems<sup>13</sup> Measurements affected by temperature and medication (vasoactive substances)<sup>13</sup> The need for intravenous contrast administration<sup>13</sup> |

**LSCI** = laser speckle contrast imaging; **MRlp** = magnetic resonance imaging perfusion; **O<sub>2</sub>C** = 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.<sup>35</sup> CEUS can be performed with a penetration depth of 4 - 15 cm.<sup>35,36</sup> Quantitative measurements are performed by determining the TTP contrast intensity.<sup>36</sup>

**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.<sup>31</sup> 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.<sup>13,38</sup> A charged coupled device camera captures a real time image.<sup>39,40</sup> ICGa provides approximately 3 – 7 mm of tissue penetration,<sup>41–43</sup> and could therefore be used as an indicator of superficial tissue perfusion.<sup>41</sup> Dedicated software can be used to analyse quantitatively ICG intensity in the entire image or in a chosen ROI.<sup>39,40,42–45</sup>

**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.<sup>39,40,42–45</sup> All studies measured ABPI and showed significant improvement after revascularisation. Colvard et al.,<sup>39</sup> Patel et al.,<sup>40</sup> and Rother et al.,<sup>42</sup> 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.<sup>44</sup> However, the studies
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. 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 possible.

| 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) | High          | Unclear                | Unclear              | Unclear        | Low               | Low        | Unclear            |
| Grözinger et al. (2014) | Unclear      | High                   | Unclear              | Low            | Low               | Low        | Low                |
| Rother et al. (2017)  | Low           | High                   | Low                  | Low            | Low               | Low        | Low                |
| Boezeman et al. (2016) | Low          | High                   | Low                  | Low            | Low               | Low        | Low                |
| Kundra et al. (2020)  | Unclear       | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Chang et al. (2020)   | Low           | Low                    | Low                  | Low            | Low               | Low        | Low                |
| Ichihashi et al. (2020) | Unclear    | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Ikeoka et al. (2016)  | High          | Unclear                | Unclear              | Low            | Low               | Low        | Low                |
| Ikeoka et al. (2020)  | High          | Unclear                | Unclear              | Low            | Low               | Low        | Low                |
| Kawarada et al. (2014) | Unclear     | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Mochizuki et al. (2016) | Unclear   | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Hinrichs et al. (2017) | High         | Low                    | Low                  | Low            | Low               | Low        | Low                |
| Jens et al. (2015)    | Low           | Unclear                | Unclear              | Unclear        | High              | Low        | Unclear            |
| Kim et al. (2017)     | Unclear       | High                   | Low                  | Low            | Low               | Low        | Low                |
| Murray et al. (2016)  | Unclear       | Unclear                | Unclear              | Low            | Low               | Low        | Low                |
| Ng et al. (2019)      | Low           | High                   | Low                  | Unclear        | Low               | Unclear    | Low                |
| Pärsson et al. (2020) | Unclear       | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Reekers et al. (2016) | Low           | Unclear                | Unclear              | Unclear        | Low               | Unclear    | Low                |
| Duerschmied et al. (2010) | High    | High                   | Unclear              | Unclear        | Low               | Low        | Low                |
| Ma et al. (2021)      | Low           | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Colvard et al. (2016) | High          | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Mironov et al. (2019) | Unclear       | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Patel et al. (2018)   | Unclear       | Unclear                | Unclear              | Unclear        | Low               | Low        | Low                |
| Rother et al. (2017)  | Low           | High                   | Unclear              | Low            | Low               | Low        | Low                |
| Rother et al. (2018)  | Low           | High                   | Low                  | Low            | Low               | Low        | Low                |
| Settembre et al. (2017) | Unclear   | High                   | Unclear              | Unclear        | Low               | Low        | Low                |
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 Becke 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.
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, Geschwandtner 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.