Near-infrared fluorescence imaging with indocyanine green in vascular surgery

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Part I

Quantification of tissue perfusion using near-infrared fluorescence imaging with indocyanine green

Chapter 2

A systematic review of the use of near-infrared fluorescence imaging in patients with peripheral artery disease

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Abstract

Objective

In the diagnosis of peripheral artery disease (PAD) the ankle brachial index (ABI) plays an important role. However, results on ABI are unreliable in patients with severe media sclerosis. Near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) can provide information about tissue perfusion and has already been studied in oncological, reconstructive and cardiac surgery. For patients with PAD, this technique might give insight in skin perfusion and thereby guide treatment. We performed a systematic review of the literature on the use of NIR fluorescence imaging in patients with PAD.

Methods

Pubmed, Medline, Embase and Cochrane were searched for articles and abstracts on the application of NIR fluorescence imaging using ICG as fluorescent dye in patients with PAD. Our search strategy combined the terms "fluorescence", "ICG" or synonyms and "peripheral artery disease" or synonyms. The extracted data include fluorescence parameters and test characteristics for diagnosis of PAD.

Results

Twenty-three articles were found eligible for this review, using 18 different parameters for evaluation of the fluorescence signal intensity. NIR fluorescence imaging was used for four main indications: diagnosis, quality control in revascularization, guidance in amputation surgery and to visualize vascular structures. For the diagnosis of PAD, NIR fluorescence imaging yields a sensitivity ranging from 67 to 100% and a specificity varying between 72 and 100%. Significant increases in multiple fluorescence parameters were found when comparing patients pre- and post-revascularization.

Conclusion

NIR fluorescence imaging can be used for several indications in patients with PAD. NIR fluorescence imaging seems promising in diagnosing PAD and guiding surgeons in treatment, especially in patients where current diagnostic methods are not applicable. Further standardization is needed to reliably use this modality in patients with PAD.

Introduction

Atherosclerotic disease of the lower limb or so called peripheral artery disease (PAD) is a common and potential life threatening disease. Besides clinical judgement, the ankle-brachial index (ABI) plays an important role in diagnosing PAD. While ABI measurement can be highly sensitive for patients with PAD, the sensitivity varies for the asymptomatic patient and is unreliable in patients with diabetes mellitus, chronic kidney disease and those with well collateralized arterial obstructions (1-3). Novel diagnostic methods that are being studied include hyperspectral imaging, positron emission tomography (PET) and multi modal magnetic resonance imaging (4). However, these methods are relatively invasive and costly when used in routine practice. Moreover, transcutaneous oxygen pressure measurement (TcPO2) can be used to measure local skin oxygenation, although the benefit of this technique in patients with PAD remains unclear (5-7). In predicting wound complications following amputation surgery, patients with a TcPO2 of less than 40mmHg tend to have an increased risk of healing complications, however, there is insufficient evidence to determine the additional value of this technique besides clinical judgement (8).

In reliably quantifying local skin and wound perfusion and to provide insight in the distribution of perfusion, the use of Near-infrared (NIR) fluorescence imaging is promising. This technique requires a source of near infrared light, a fluorescent dye and a camera that measures the emission of near infrared light (9). It has already been used for various indications including image guidance in oncologic surgery, intra-operative perfusion measurement of bowel anastomosis to predict leakage, location of perforator vessels in reconstructive surgery and as quality control for coronary artery bypass surgery (10-19). Indocyanine green (ICG) is one of the two fluorescent dyes approved for clinical use by the food and drug administration (FDA) and is confined to vascular components making it feasible for skin perfusion assessment using either an intravenous or intra-arterial route (11, 20, 21). The toxicity of ICG is low with a reported incidence of allergic reactions in 1 out of 10.000 patients (11). After administration of the fluorescent dye, the camera creates an image of the measured fluorescence intensity signals in the area recorded, i.e. the region of interest (ROI) (20). After measuring intensities over time, a time-intensity curve can be visualized, which can be derived from diverse fluorescence parameters (22). Measurement of a time-intensity curve using ICG, which has a half-life of 150 to 180 seconds, usually takes up to five minutes (11). The resulting intensity signals are influenced by several factors, including type and amount of fluorescent tracer used, excitation light delivery mode, camera distance and fluorescence light collection (9). Patient related factors influencing the intensity signals include the presence of inflammation or ulcers, edema, skin type and possibly the haemodynamic status. NIR fluorescence imaging is a relatively new technique with potential utility in vascular

surgery and might be of beneficial use in patients with PAD. The aim of this review was to outline the current research in the field of NIR fluorescence imaging in patients with PAD and to provide directions to standardize the use of this modality.

Methods

Search strategy

A literature search was performed in major databases (Pubmed, Medline, Embase and Cochrane) for articles on the application of NIR fluorescence imaging in patients with peripheral artery disease, published before March 2018. Our search strategy combined the terms "fluorescence" or "ICG" or synonyms with "peripheral artery disease" or synonyms. The full text of the search strategy is available in Appendix A. Articles were systematically screened by a two-stage method, whereby the title and abstract were screened first, which was subsequently followed by full-text screening.

Article selection

Only full text articles in English were included in this review and articles reporting use of NIR fluorescence in animals were excluded. Article selection was performed by two independent researchers (PH and SO). All articles describing the use of NIR fluorescence imaging in patients with peripheral arterial disease were included. Since this technique can be used for different applications, the results were divided in four categories, consisting of the main applications: 1. diagnosis 2. quality control following revascularization 3. amputation and 4. NIR fluorescence angiography.

Quality assessment

The quality and the risk of bias of the included articles were independently evaluated by two reviewers (PH and SO) in according to the revised quality assessment of diagnostic accuracy studies (QUADAS-2) (23). In case of discrepancies in interpretation, a third reviewer (LM) was asked to adjudicate.

Data extraction

For all articles, data extracted consisted of the relevant patient characteristics, name of fluorescence camera system and used ICG concentration, (the effect of revascularization on) measured fluorescence parameters, correlated (imaging) modalities, and the diagnostic value (sensitivity and specificity) of NIR fluorescence imaging compared to current standards. Fluorescence parameters were standardized to provide a better overview.

Results

Overview of studies

An overview of the article selection for this systematic review is reported in a flow diagram according to the PRISMA-P 2015 guidelines (Figure 1) (24). A total of 944 articles were found of which eventually 23 articles were eligible for the review. The results of the quality assessment are illustrated in Table I and Figure 2. All articles in this review used ICG as fluorescent marker. To obtain an objective assessment of the fluorescence intensity measurements, different parameters were used, as summarized in Table II. In the selected studies a total of 18 parameters were utilized. Most studies included in this review used time dependent parameters. By measuring the fluorescence intensity over time in a selected ROI, a time-intensity curve can be plotted (Figure 3) (25).

NIR fluorescence imaging was used in 9 studies as a diagnostic modality, whereas 10 studies determined its use in quality control after revascularization procedures. Six studies described the use of this perfusion measurement in patients undergoing amputation surgery. Furthermore, NIR fluorescence imaging is used in two studies for visualization of vascular structures, hereafter stated as NIR fluorescence angiography. An overview of the included studies with study characteristics, diagnostic value for detection of PAD and/or results on quality control following revascularization is provided in Table III.

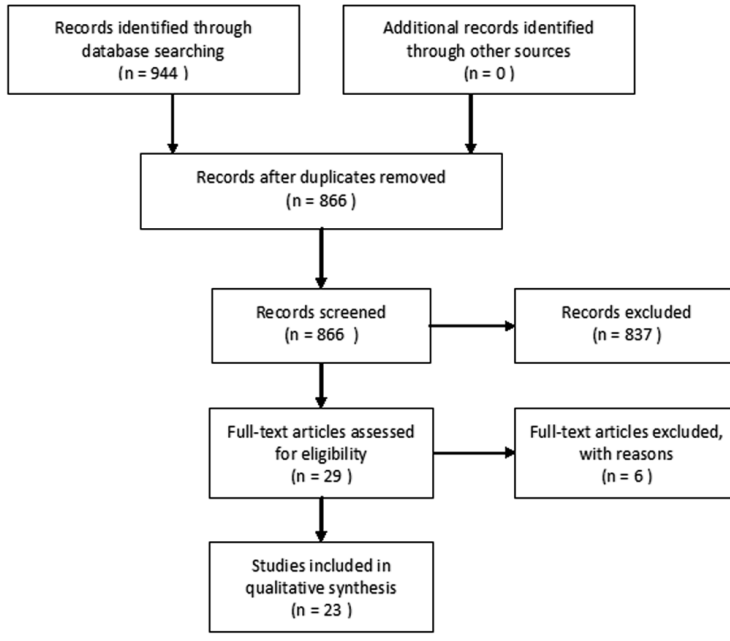

Figure 1. Prisma flowchart for selection of included studies.

Table I. Quality assessment and risk of bias according to QUADAS-2. Low risk of bias (-), high risk of bias (+), risk of bias unclear (?).

Study	Risk of bias				Applicability concerns		
	Patient selections	**Index test**	**Reference standard**	**Flow and timing**	**Patients selection**	**Index test**	**Reference standard**
Igari et al. 2013 (1)	-	+	-	-	-	-	-
Zimmermann et al. 2012 (6)	-	+	-	-	-	-	-
Yamamoto et al. 2012 (18)	-	-	-	-	-	-	-
Joh et al. 2016 (20)	-	+	+	?	-	-	+
Igari et al. 2014 (21)	-	+	-	-	-	-	-
Braun et al. 2013 (22)	-	+	-	-	-	-	-
Igari et al. 2014 (26)	+	+	-	-	+	-	-
Nishizawa et al. 2016 (27)	?	+	-	-	+	+	-
Kang et al. 2010 (28)	-	+	-	-	-	-	-
Kang et al. 2010 (29)	+	+	-	-	-	-	-
Terasaki et al. 2013 (30)	-	+	-	-	-	-	-
Venermo et al. 2016 (31)	-	+	-	-	-	-	-
Colvard et al. 2015 (32)	-	+	-	-	-	-	-
Rother et al. 2016 (33)	-	+	-	-	-	-	-
Settembre et al. 2017 (25)	-	+	-	-	-	-	-
Riess et al. 2017 (34)	-	+	-	-	-	-	-
Rother et al. 2018 (35)	-	+	-	-	-	-	-
Perry et al. 2012 (36)	+	+	?	-	-	-	?
Samies et al. 2015 (37)	+	+	?	?	-	-	?
Zimmermann et al. 2010 (38)	-	-	?	-	-	-	?
Yang et al. 2018 (39)	-	-	?	-	-	-	?
Unno et al. 2008 (40)	-	+	-	-	-	-	-
Sumpio et al. 2013 (41)	?	?	?	?	?	?	?

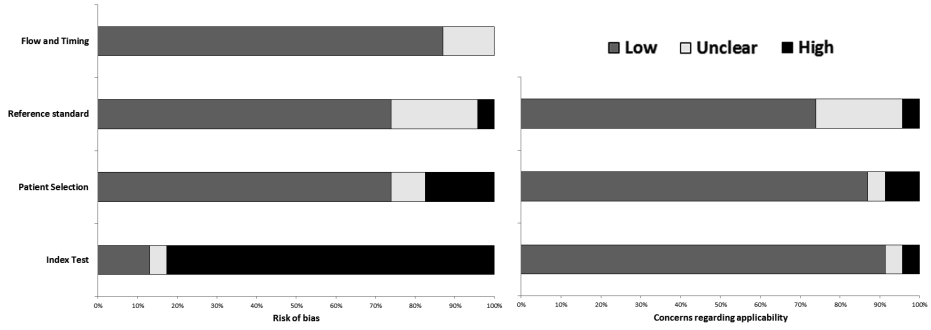

Figure 2. Proportion of studies with low, high and unclear risk of bias according to QUADAS-2.

Table II. Overview of used fluorescence parameters in current literature.

Parameter	Definition (unit)	Equivalents	Reference(s)
FI	Fluorescence intensity as calculated by used software (AU)	-	(1, 6, 10, 20-22, 25-41, 43)
Ingress	Magnitude of increase from baseline to peak fluorescence intensity (AU)	Imax, Maximum Peak Intensity, Maximum Intensity	(1, 6, 21, 22, 25-27, 32, 33, 35)
Ingress rate	Rate of FI increase from baseline to maximum FI (AU/s)	Slope, Intensity Rate	(1, 22, 25, 32-35)
Egress	Magnitude of FI decrease from maximum FI to end FI (AU)	-	(22)
Egress rate	Rate of FI decrease from maximum FI to end FI (AU/s)	Washout Kinetics	(22, 29, 32)
Tmax	Time until maximum FI (s)	Time To Peak, Peak Intensity Time	(1, 10, 21, 26, 27, 29, 43)
T1/2	Time until half of maximum FI (s)	-	(1, 21, 26, 27, 30, 31, 41, 43)
Starting FI	FI upon start ICG administration (AU)	-	(22)
PDE10	FI 10 seconds following rise of FI (AU)	SPY10	(1, 25, 30, 31, 41)
Perfusion Rate	Blood exchanged per minute (%/min)	-	(28)
Filling	Time following administration of ICG and first FI signal (s)	-	(29)
Perfusion Index	Slope of fluorescence intensity increase (%)	-	(6)
Curve Integral	Area under the curve of time-intensity curve	-	(22)
End Intensity	FI at end of study (AU)	-	(22)
Td90%	Time until 90% decrease in maximum FI (s)	-	(26, 27)
Td75%	Time until 75% decrease in maximum FI (s)	-	(26)
IR60	Rate of FI measured 60 seconds after Tmax (AU/AU)	-	(26)
RPV	Percentage of maximum fluorescence intensity obtained (%)	-	(39)

Abbreviations: FI = Fluorescence Intensity, AU = Arbitrary Units, s = seconds, PDE = PhotoDynamicEye.

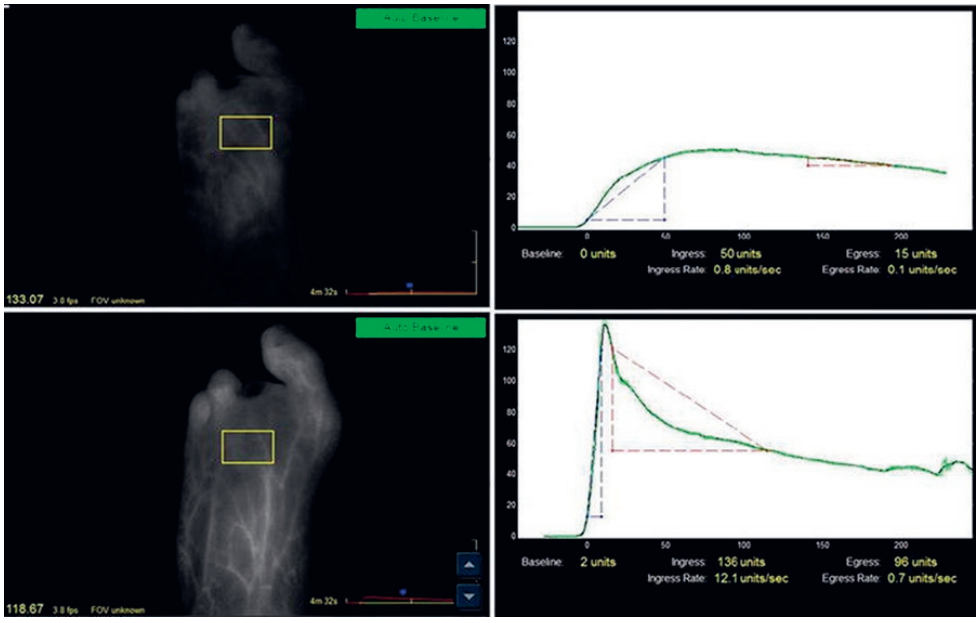

Figure 3. Fluorescence images with selected region of interest and corresponding time-intensity curves before (upper panel) and after revascularization (lower panel). Reprinted by permission from Springer Nature: World Journal of Surgery (25). © 2017.

NIR fluorescence imaging as diagnostic modality

During the past years, the role of NIR fluorescence imaging as diagnostic modality for PAD has been determined in several studies, which evaluated quantitative parameters for the diagnosis of PAD and compared these parameters with other diagnostic modalities (1, 6, 21, 26-31). Measured test accuracies for diagnosing PAD using NIR fluorescence imaging are depicted in Table III. Kang et al. first described the use of NIR fluorescence imaging in a patient with symptomatic PAD and compared these to a patient with normal results on ABI (29). The perfusion rate, defined as the percentage of blood exchanged per minute, was measured at the dorsum of both feet. A clear definition of this parameter is stated elsewhere (42). All measured outcomes, also including time to filling, time to maximum intensity and washout kinetics were worse in the patient with symptomatic PAD (data not shown in table). Two studies compared different ICG parameters in patients with - and without PAD, in which PAD was defined as a stenosis of >50% in one or more peripheral arteries (26, 28). Kang et al. showed a significantly lower perfusion rate in patients with PAD (16.6 vs 38.1 %/min) (28). In diagnosing PAD, a cut-off perfusion rate of 24.4 %/min was able to predict PAD with a sensitivity of 92%. Igari et al. found other parameters associated with PAD including Td90% and

Td75%, of which the Td90% was the most significant parameter (P=0.001) (26). A cut-off value of 25 seconds was able to predict an infrapopliteal lesion with a sensitivity of 82.6%.

NIR fluorescence imaging was also compared with currently available diagnostic modalities (ABI, TcPO2, toe pressure (TP), toe brachial index (TBI) and ankle pressure (AP) for the detection of critical limb ischemia (CLI). CLI was defined as either a Rutherford grade ≥ 4 or Fontaine stage ≥ 3 (6, 27, 30, 31). A cut-off perfusion index of 59% was able to predict CLI with a sensitivity of 100% and a specificity of 83.3% (6). Terasaki et al. compared NIR fluorescence imaging to TcPO2 measurement, showing an overall moderate correlation (R^2=0.50) (30). A cut-off value of 28 arbitrary units for PDE10 predicted CLI, defined as TcPO2 <30 mm Hg, with a sensitivity of 100% and specificity of 86.6%. T1/2 showed significant difference in patients with Fontaine stage 2 and 3, however no significance was seen between Fontaine stage 2 and 4. In patients with diabetes mellitus a good reliability was found for NIR fluorescence imaging by comparing two separate measurements in patients with CLI (31). A moderate correlation between NIR fluorescence and TcPO2 was found being stronger in a subgroup of patients with diabetes mellitus. Setting 21 arbitrary units for PDE10 as cut-off, CLI was predicted with a sensitivity of 67% and a specificity of 72%. T1/2 turned out to be a good NIR fluorescence parameter after correlating to the ABI and TP. When performing NIR fluorescence imaging using an intra-arterial injection of ICG, Igari et al found the measured T1/2 was able to predict an ABI lower than 0.70 with a sensitivity of 85% and a specificity of 100% (21). In another study, they compared NIR fluorescence to TP and showed a sensitivity of 77% using a cut-off value of 20 seconds for the T1/2 to predict a toe pressure less than 50mmHg (1). In a study by Nishizawi et al. in 2015, results of NIR fluorescence imaging were compared between PAD patients with or without dialysis treatment in which results of 20 dialysis patients were compared to 42 non-dialysis patients (27). A significant difference in Td90% was found in two of the three ROIs comparing patients with and without dialysis. Tmax and Td90% showed significant differences in patients with CLI compared to patients without CLI. No comparison was made to conventional diagnostic modalities.

Conclusion

The accuracy in diagnosing PAD or CLI using NIR fluorescence imaging ranged from 67 to 100% with corresponding specificities of 72 to 100%. Time-related parameters, including T1/2, PDE10 and Td90%, showed to be the most statistically significant parameters in varying ROIs.

Table III. Overview of study characteristics and results on NIR fluorescence imaging.

Application	**Reference**	**Study characteristics**				**Diagnostic value of detecting PAD and/or CLI**			**Fluorescence parameters in revascularization control**
		Patients (limbs)	Diabetes (N)	ICG dosage	Comparing modality	Fluorescence parameter	Sensitivity (%)	Specificity (%)	
Diagnostic modality									
	Kang et al. 2010 (29)	2	-	0.16 mg/kg	-	-	-	-	-
	Kang et al. 2010 (28)	29 (56)	3	0.16 mg/kg	ABI	Perfusion rate	0.92	0.90	-
	Zimmermann et al. 2012 (6)	30 (30)	9	0.5 mg/kg	ABI	Perfusion index	1.00	0.83	-
	Terasaki et al. 2013 (30)	34 (34)	19	0.1 mg/kg	TcPO2	PDE10	1.00	0.87	-
	Igari et al. 2013 (1)	21 (23)	9	0.1 mg/kg	ABI, TAI, TP	T1/2	0.77	0.80	-
	Igari et al. 2014 (21)	16 (22)	6	0.01 mg/kg	ABI, AP, TAI, TP	T1/2	0.85	1.0	-
	Igari et al. 2014 (26)	23 (38)	19	0.1 mg/kg	ABI, TAI, TP	Td90%	0.83	0.73	-
	Venermo et al. 2016 (31)	41 (41)	19	0.1 ml/kg	ABI, TP, TcPO2	PDE10	0.67	0.72	-
	Nishizawa et al. 2016 (27)	62	39	0.1 ml/kg	-	-	-	-	-
Quality control in revascularization									
	Perry et al. 2012 (36)	1	1	12.5 mg	-	-	-	-	-
	Braun et al. 2013 (22)	24 (26)	22	12,5 mg	ABI, TP	-	-	-	Ingress: P=0.004 Ingress rate: P= 0.015 Curve integral: P= 0.021 End intensity: P= 0.019 Egress: P= 0.004 Egress rate: P= 0.013

Table III. Continued

Application	Reference	Study characteristics			Diagnostic value of detecting PAD and/or CLI				Fluorescence parameters in revascularization control
	Sumpio et al. 2013 (41)	2	-	-	TcPO2	-	-	-	-
	Igari et al. 2013 (1)	21 (23)	10	0.1 mg/kg	ABI, TBI, TP	-	-	-	Ingress: P<0.0001 Tmax: P=0.001 Ingress rate: P<0.0001 T1/2: P=0.005 PDE10: P=0.0001
	Colvard et al. 2016 (32)	93	65	2.5 ml	ABI	-	-	-	Ingress: P<0.001 Egress: P= 0.035
	Joh et al. 2016 (20)	4	2	3-5 ml	-	-	-	-	-
	Rother et al. 2017 (33)	33	13	0.1 ml/kg	ABI	-	-	-	Ingress: P<0.001 Ingress rate: P<0.001
	Settembre et al. 2017 (25)	101 (104)	56	0.1 mg/kg	ABI, TP	-	-	-	Mean intensity: P=0.001 SPY10: P<0.001
	Riess et al. 2017 (34)	7	3	0.1 mg/kg	ABI, PPG	-	-	-	Ingress rate: P=0.005
	Rother et al. 2018 (35)	40	16	0.1 mg/kg	ABI	-	-	-	Ingress: P<0.001 Ingress rate: P=0.001
Amputation surgery									
	Zimmermann et al. 2010 (38)	10	6	0.5 mg/kg	-	-	-	-	-
	Perry et al. 2012 (36)	1	1	12.5 mg	-	-	-	-	-
	Sumpio et al. 2013 (41)	2	-	-	TcPO2	-	-	-	-
	Samies et al. 2015 (37)	2	2	-	-	-	-	-	-
	Joh et al. 2016 (20)	4	2	3-5 ml	-	-	-	-	-
	Yang et al. 2018 (39)	13 (17)	11	10 mg	-	-	-	-	-

Table III. Continued

Application	Reference	Study characteristics				Diagnostic value of detecting PAD and/or CLI			Fluorescence parameters in revascularization control
Angiography									
	Unno et al. 2008 (40)	9	-	1 ml	-	-	-	-	-
	Yamamoto et al. 2017 (18)	12	-	0.05 mg/kg	TTF	-	-	-	-

Abbreviations: ABI = Ankle Brachial Index, TAI = Toe Arm Index, TP = Toe Pressure, AP = Ankle Pressure, TcPO2= Transcutaneous oxygen pressure measurement, TTF = Transit Time Flowmetry, PPG = Photoplethysmography.

NIR fluorescence imaging as quality control in revascularization

NIR fluorescence imaging provides the possibility to measure direct effect of revascularization on regional perfusion and can be performed intra-operatively or directly following endovascular revascularization (Figure 3). Ten studies, of which were three case studies, performed NIR fluorescence imaging for evaluating the effect of endovascular and open revascularization on the fluorescence parameters in a study population varying between 1 and 101 patients (Table III).

In 2013, Braun et al. performed a cohort study in which NIR fluorescence imaging was performed within five days following revascularization in patients with PAD in Rutherford stage 5 or 6 (22). In thirteen patients, NIR fluorescence imaging was performed before and after revascularization. In these patients, there was a significant improvement in ingress, ingress rate, AUC, end intensity, egress and egress rate (all $P<0.05$). A significant correlation was found between ABI and ingress, ingress rate and egress rate (all $P<0.05$). Furthermore, in the last years, 6 studies with cohorts of 7 or more patients were performed, including endovascular as well as open revascularization (1, 25, 32-35). In these studies, improvement of outcome on several but not all fluorescence parameters was seen, in contrary to ABI, which showed significant improvement in all studies. Interestingly, when comparing pre and post interventional results on NIR fluorescence imaging in a subset of patients, who showed no clinical improvement in symptoms, no statistically significant differences ($P>0.05$) were found for the measured parameters (25, 32). The only study comparing pulse volume recordings pre- and postrevascularization found significant improvement in only one of two measured parameters (34). The measured ingress rate in this study showed significant improvement following revascularization ($P=0.005$). In a recent study the concept of angiosomes was studied by comparing NIR fluorescence parameters among four different angiosomes following single vessel outflow tibial bypass surgery. Significant improvement was seen in directly as well as indirectly revascularized angiosomes ($P<0.001$) (35). Interestingly, in a subset of patients with diabetes mellitus, the directly revascularized angiosomes showed tendency towards a better improvement on perfusion measurement compared to indirectly revascularized angiosomes ($P=0.098$).

Conclusion

Multiple NIR fluorescence parameters statistically improved upon successful revascularization, thereby showing possible benefit for use of this technique as quality control. The absence of improvement of NIR fluorescence parameters in patients without successful revascularization supports this hypothesis. Furthermore, NIR fluorescence imaging is a promising method to further investigate the relevance of angiosomes in guiding treatment.

NIR fluorescence imaging as guidance in amputation surgery

For patients with PAD, NIR fluorescence imaging might be able to predict outcome of wound healing and viability of skin flaps in amputation surgery and may therefore be useful in intra-operative determination of amputation levels. Six studies evaluated the use of NIR fluorescence imaging on predicting viability. In a case report by Perry et al., NIR fluorescence imaging was used intra-operatively to measure perfusion of the foot following tibial bypass surgery (36). NIR fluorescence intensity was measured at the foot following a femoral-tibial bypass and showed a perfusion deficit of the fourth digit and plantar side of the fourth metatarsal. Upon manual occlusion of the bypass, no signal was found in the third and fifth digit either. Amputation of the fourth digit and debridement of the plantar side of the fourth metatarsal was performed followed by primary closure of the wound. NIR fluorescence imaging as guidance for amputation surgery was also described in case series (20, 37). Measurements of fluorescence intensities all showed good intensity signals of the well-perfused parts of the foot, whereas less-perfused parts showed a well demarcated deficit in signal intensity (Figure 4) (20). After amputation of the necrotic digits, postoperatively performed NIR fluorescence intensity measurement showed good perfusion of the remaining tissue. In all case studies, no postoperative complications occurred regarding the healing of the wound.

In one cohort study of 10 patients undergoing amputation surgery, NIR fluorescence imaging was able to predict wound complications in 3 patients. Except for one patient with a thrombus in the amputation wound, no complications occurred in patients without fluorescence intensity deficit (38). Comparison of NIR fluorescence parameters with clinical judgement of necrosis was performed in a retrospective cohort of 13 patients undergoing 17 amputations (39). Absolute values for fluorescence intensity proved low sensitivity and specificity in predicting skin viability. Using relative perfusion values, a value of less than 31% was able to predict viability with a sensitivity of 100%.

Conclusion

NIR fluorescence imaging might be of use in predicting postoperative wound complications. Predicting the level of amputation could be a possible application of NIR fluorescence imaging, which has not yet been studied. The additional value of this method besides clinical judgement in predicting flap viability has yet to be identified.

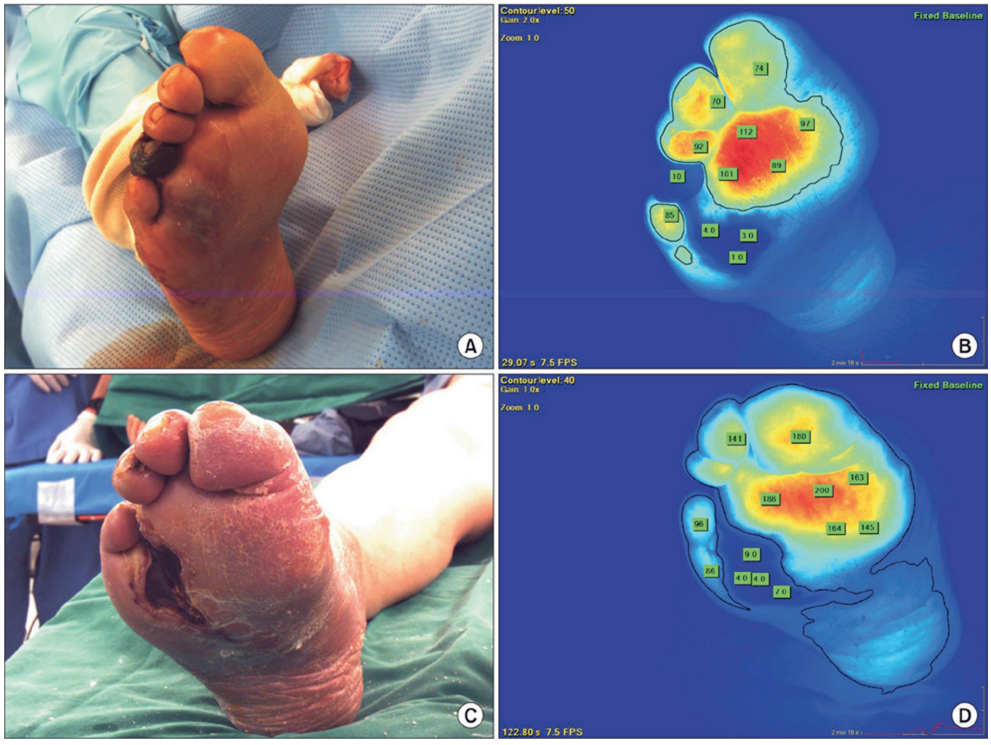

Figure 4. NIR Fluorescence intensity images. *Upper panel:* color image of right foot, showing a necrotic dig. 4 before surgical intervention (A) and the corresponding NIR fluorescence image (B). *Lower panel:* Color (C)and NIR fluorescence image (D) after amputation of dig. 4, showing viable tissue. Reprinted from Joh et al., Annals of Surgical Treatment and Research (2016) (20).

NIR fluorescence angiography

The use of NIR fluorescence imaging as modality to visualize vascular structures in patients with PAD has been described in two studies (10, 40). In these two studies, NIR fluorescence was used intra-operatively in peripheral artery bypass surgery to obtain information about the bypass. In these studies, with cohort sizes of 9 and 12 patients, NIR fluorescence imaging revealed decreased fluorescence intensity in two patients. In one patient, revision of the bypass was performed after revealing decreased intensity over the distal anastomosis. In the other patient, decreased signal was found over the outflow artery, which was confirmed by Transit Time Flowmetry (TTF).

Conclusion

NIR fluorescence angiography has been studied in a small cohort of patients. These studies have shown a possible application of this technique, e.g. to assess for bypass patency, however the added value besides clinical judgement and TTF is controversial.

Discussion

This systematic review shows the variety of indications for the use of NIR fluorescence imaging in patients with peripheral artery disease, including peripheral perfusion measurement for diagnosis, quality control in revascularization and for guidance in amputation surgery. Furthermore it is possible to visualize vascular structures. The use of NIR fluorescence imaging in diagnosing PAD yields a sensitivity up to 100% and is thereby not limited by media sclerosis as is seen in selected patients with diabetes mellitus and chronic kidney disease (6, 30). NIR fluorescence imaging can be performed in multiple ROIs and also a variety of parameters can be calculated using this technique, providing a real-time perfusion map of the imaged area. For quality control in revascularization, multiple parameters have shown to improve upon successful revascularization (1, 20, 22, 25, 32-36, 41). Furthermore, the absence of intensity signal measured by NIR fluorescence imaging is able to guide surgeons in performing targeted amputations, as was shown in five described case series (20, 36-38, 41). As stated earlier, most current diagnostic methods for patients with PAD focus on detecting morphological and anatomical deviations in the macrocirculation. Segmental pressure readings, Doppler waveforms and pulse volume recordings enhance the sensitivity of the ankle-brachial index for diagnosing PAD, however they do not provide information about regional tissue perfusion. The role of TcPO2 measurement to measure skin perfusion remains controversial and definitive cut-off values to guide physicians have yet to be stated (5, 7, 8). New modalities to measure skin perfusion include hyperspectral imaging, nuclear imaging and magnetic resonance imaging, but the benefit of these modern technologies has yet to be established (5, 34, 44).

NIR fluorescence imaging is able to assess the intensity signal that is the mere equivalent of skin perfusion and has already proven its feasibility and safety within different medical fields, e.g. oncologic surgery, reconstructive surgery and cardiac surgery. Studies included in this systematic review show significant correlations between fluorescence parameters and conventional methods such as ankle-brachial indices and toe pressures which gives tendency towards good reliability of NIR fluorescence imaging in diagnosing PAD. This technique might therefore be of adjunctive use in diagnosing PAD. Moreover, intra-operative use of this technique provides a new possibility to guide surgeons and radiologists in performing additional revascularization procedures or prevent unnecessary interventions. In amputation surgery, it is possible to measure intensity signals in the overlying skin flap and thereby provide information about healing tendencies or even guide intra-operative decision making. Besides improving patient outcome by reducing the amount of unnecessary interventions, this technique might also reduce costs. Cooperating with different medical fields where NIR fluorescence imaging has proven feasible helps justify the use of this costly system. NIR fluorescence imaging using ICG requires intravascular access, which might preclude easy use in the outpatient clinic. As is concerned for the technique of NIR fluorescence imaging, different camera systems can be used of which an overview is given in a review article by Dsouza et al. (45). For the clinical use of NIR fluorescence imaging, it is important to consider system- and patient related factors possibly influencing fluorescence signals. Since the penetration depth of NIR is limited up to 1 cm, no information can be obtained about perfusion of deeper underlying tissues (46). However, diminished blood supply will likely result in diminished perfusion of the skin and underlying subcutaneous tissue first. To improve reliability, further standardization of all possible intervening variables is necessary to provide a reliable and valid measurement of perfusion using NIR fluorescence imaging. Furthermore, this review shows the heterogeneity in ROIs that are used and variety of parameters used for quantitative assessment of perfusion. As stated by Igari et al., time-related parameters appear to have greater diagnostic accuracy than fluorescence intensity, especially since fluorescence intensity alone is influenced by multiple factors (9, 26). This statement is supported by this review, which shows highest diagnostic accuracies are found when using time-related parameters, such as T1/2, PDE10 and Td90%. Which parameter in which ROI provides the most reliable outcome in diagnosing PAD has yet to be established. Further studies should therefore focus on validating NIR fluorescence measurement by using a standardized protocol. These studies should minimize bias by incorporating subsets of patients (e.g. patients with diabetes mellitus or chronic kidney disease) and compare these results with conventional diagnostic methods. As is concerned for quality control following revascularization, further studies should compare changes in fluorescence parameters pre- and postrevascularization to conventional methods and clinical outcome. A valid and reliable measurement of perfusion using NIR fluorescence imaging can guide decision making and thereby improve patient outcome. This systematic review provides

an overview of the clinical use of NIR fluorescence imaging in patients with peripheral artery disease. The main limitation of this study is the heterogeneity of included studies, which precludes a comparative analysis. This supports the need for standardization of protocols for NIR fluorescence imaging in patients with PAD.

Conclusion

NIR fluorescence imaging can be of additional diagnostic value in patients with PAD, especially where current methods are not applicable. The intra-operative use of this technique shows promising results on predicting outcome following revascularization and might prevent unnecessary interventions. Future studies should focus on standardizing diagnostic protocols, with a focus on NIR fluorescence measurement, fluorescence parameters and ROIs.

Appendices

Appendix A. Search strategy.

((“Fluorescence”[Mesh] OR “fluorescence”[tw] OR fluorescen*[tw] OR “Indocyanine Green”[Mesh] OR “Indocyanine Green”[tw] OR “ICG”[tw] OR “Fluorescein Angiography”[Mesh] OR Fluorescein*[tw]) AND (“Peripheral Arterial Disease”[Mesh] OR “Peripheral Arterial Disease”[tw] OR “Peripheral Arterial Diseases”[tw] OR “Peripheral Artery Disease”[tw] OR “Peripheral Artery Diseases”[tw] OR “Peripheral Vascular Diseases”[mesh:noexp] OR “Peripheral Vascular Disease”[tw] OR “Peripheral Vascular Diseases”[tw] OR “Peripheral Vessel Disease”[tw] OR “Peripheral Vessel Diseases”[tw] OR “limb ischaemia”[tw] OR “limb ischemia”[tw] OR (“Ischemia”[mesh] AND “Leg”[mesh]) OR ((ischemi*[tw] OR ischaemi*[tw]) AND (“leg”[tw] OR “legs”[tw] OR “limb”[tw] OR “limbs”[tw] OR hindlimb*[tw])) OR “Arteriosclerosis Obliterans”[mesh] OR “arteriosclerosis obliterans”[tw] OR peripheral arter*[tw] OR “peripheral vascular”[tw] OR peripheral vessel*[tw] OR (“Extremities”[mesh] AND “Arterial Occlusive Diseases”[Mesh]))) NOT (“Animals”[mesh] NOT “Humans”[mesh]).

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