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Near-infrared fluorescence imaging with indocyanine green in vascular surgery

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Part II

Clinical translation of quantitative tissue perfusion assessment using near-infrared fluorescence imaging with indocyanine green in lower extremity arterial disease

Chapter 7

Near-infrared fluorescence imaging with indocyanine green for quantification of changes in tissue perfusion following revascularization

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Abstract

Introduction

Current diagnostic modalities for patients with peripheral artery disease (PAD) mainly focus on the macrovascular level. For assessment of tissue perfusion, near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) seems promising. In this prospective cohort study, ICG NIR fluorescence imaging was performed pre- and post-revascularization to assess changes in foot perfusion.

Methods

ICG NIR fluorescence imaging was performed in 36 patients with PAD pre- and postintervention. After intravenous bolus injection of 0.1mg/kg ICG, the camera registered the NIR fluorescence intensity over time on the dorsum of the feet for 15 minutes using the Quest Spectrum Platform®. Time-intensity curves were plotted for 3 regions of interest (ROIs): 1. The dorsum of the foot, 2. The forefoot and 3. The hallux. Time-intensity curves were normalized for maximum fluorescence intensity. Extracted parameters were the maximum slope, area under the curve (AUC) for the ingress and the AUC for the egress. The non-treated contralateral leg was used as a control group.

Results

Successful revascularization was performed in 32 patients. There was a significant increase for the maximum slope and AUC egress in all three ROIs. The most significant difference was seen for the maximum slope in ROI 3 (3.7 %/s to 6.6 %/s, $p<0.001$). In the control group, no significant differences were seen for the maximum slope and AUC egress in all ROIs.

Conclusions

This study shows the potential of ICG NIR fluorescence imaging in assessing the effect of revascularization procedures on foot perfusion. Future studies should focus on the use of this technique in predicting favourable outcome of revascularization procedures.

Introduction

Peripheral artery disease (PAD) is amongst the most frequent vascular diseases worldwide and most often involves atherosclerotic disease of the lower extremities, so called lower extremity arterial disease (LEAD) (1). In diagnosing LEAD, the ankle-brachial systolic pressure index (ABI) is a valuable tool (2). However, the use of this technique is limited in patients with severe media calcinosis or previous amputation (3). Furthermore, the ABI as well as other diagnostic methods including toe pressure measurement (TP), computed tomography angiography (CTA) and digital subtraction angiography (DSA) focus on macrovascular aspects of lower extremity circulation. Especially in patients with chronic limb-threatening ischemia (CLTI), reliable information about tissue perfusion in the area of interest can be of paramount importance in guiding revascularization procedures (3). In assessing the effect of revascularization procedures, physicians focus on clinical judgement of the foot, thereby supported by changes in ABI, TP, and macrovascular changes as seen on DSA. Objective assessment of the changes in tissue perfusion remains unknown. Several imaging techniques have been examined for quantification of tissue perfusion in patients with LEAD, including Single Photon Emission Computed Tomography and Hyperspectral Imaging (4, 5). In a recent systematic review, the use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) to measure tissue perfusion in patients with PAD was reviewed (6). This imaging modality has already been used extensively in other medical fields for imaging and perfusion assessment, including oncologic, cardiac and reconstructive surgery (7, 8). In reconstructive surgery, perfusion assessment with ICG NIR fluorescence imaging shows promising results in predicting tissue viability (9). Measurement of tissue perfusion using NIR involves a camera that measures light in the NIR spectrum, allowing the visualization of a specific intravascular administered fluorophore: ICG. This fluorophore is confined to vascular components and therefore feasible to assess tissue perfusion. The use of this technique in patients with LEAD seems promising, especially for quality control following revascularization (6, 10-12). In a recent study by Settembre et al., 101 patients underwent NIR fluorescence imaging pre- and post-revascularization (10). A significant improvement in ingress rate (i.e. rate of fluorescence intensity increase) was seen for patients undergoing technically successful revascularization. The effect of revascularization on the contralateral non-treated leg was described in one study with 21 patients undergoing unilateral revascularization (13). In this study, ICG NIR fluorescence imaging showed a significant decrease in NIR fluorescence intensity and inflow time on the non-treated side. Whether these findings can be explained by an actual decrease in contralateral foot circulation has yet to be identified. Providing physicians with an instrument to objectively assess the effect of revascularization on tissue perfusion can guide treatment strategies and possibly predict favorable outcomes following revascularization. This requires the use of a standardized protocol for ICG NIR fluorescence imaging with the use of standardized parameters. This prospective cohort study incorporated the use of beforementioned standardized protocol in patients before- and after revascularization. Furthermore, a recommendation is given for the standardized analyses of measured NIR fluorescence intensities in future studies.

Methods

This prospective cohort study was approved by the Medical Research and Ethics Committee of the Leiden University Medical Center and registered in the Dutch Trial Register with number NL7531. Patients undergoing revascularization procedures for LEAD from December 2018 until January 2021 were included in a single, academic hospital in the Netherlands. Informed consent was obtained in all patients. ICG NIR fluorescence imaging was performed pre- and post-revascularization. All post measurements were performed within 7 days of the initial procedure. ABI and TP were measured in all patients. Exclusion criteria, based on contra-indications for ICG, were: allergy to iodine or ICG, hyperthyroidism or thyroidal adenoma, pregnancy, kidney failure (eGFR <45) and liver failure.

NIR fluorescence imaging measurement

The Quest Spectrum Platform® (Quest Medical Imaging, Middenmeer, The Netherlands) was used to perform ICG NIR fluorescence imaging. This system is capable of measuring both visible light as well as the NIR signal of ICG. A dose of 0.1mg/kg of ICG was administered intravenously and subsequently, the NIR fluorescence intensity was measured in both feet. Upon intravenous administration of ICG, the camera, targeted to the area of interest, measured the fluorescence intensity over time (Figure 1). The protocol used for ICG NIR fluorescence imaging in this study is displayed in Figure 2.

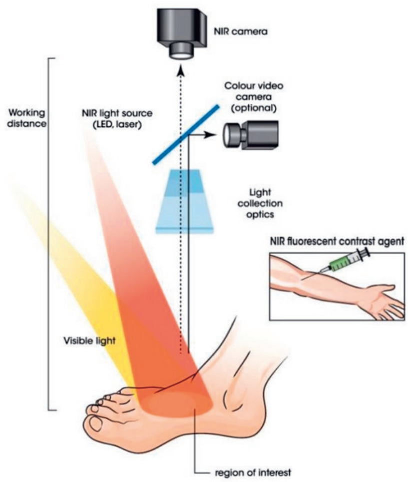

Figure 1. Near-infrared fluorescence imaging with indocyanine green setup.

Protocol near-infrared fluorescence imaging with indocyanine green
1. Confirm in- and exclusion criteria.
2. Patient in supine position with room temperature of 20-25 degrees Celsius.
3. Measure blood pressure, ankle-arm index and toe pressure.
4. Position feet of patients against a dark background board.
5. Position camera at 50 cm distance perpendicular to dorsum of feet.
5. Clear room of visible light.
6. Administer 0.1mg/kg indocyanine green intravenously with a minimum of 2.5mg.
7. Record near-infrared fluorescence for 15 minutes.

Figure 2. Protocol near-infrared fluorescence imaging with indocyanine green.

Data analyses

The Quest Research Framework® (Quest Medical Imaging, Middenmeer, The Netherlands) was used to create and analyse the time-intensity curves. Time-intensity curves were normalized for maximum fluorescence intensity. The extracted parameters were measured in three ROIs (i.e. the dorsum of the foot, the forefoot and the hallux) and included: maximum slope (%/s), area under the curve (AUC) for the ingress (%), and the AUC for the egress after 180 seconds (%) (Figure 3). Improvement of perfusion was defined as an increase of inflow parameters (slope and AUC ingress) and an improvement in egress time (AUC egress). Data was analysed using IBM SPSS Statistics 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA). Pre- and post-intervention results were compared using the Wilcoxon Rank Sign test.

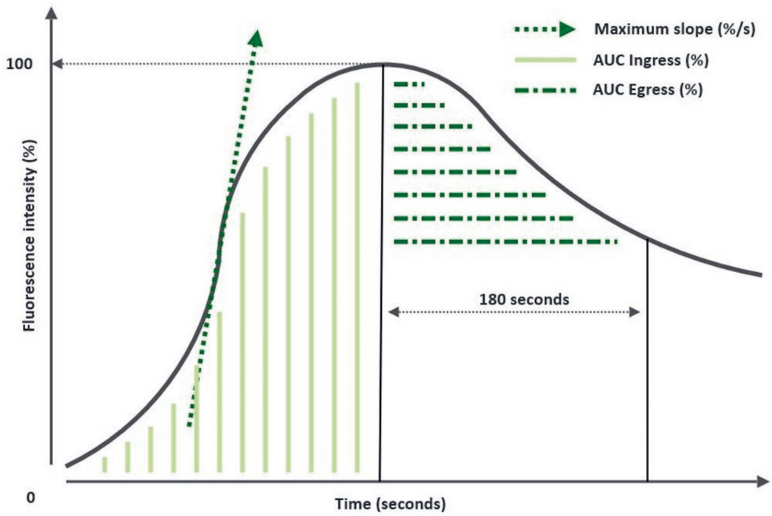

Figure 3. Normalized time-intensity curve with extracted parameters.

Results

During the study period, successful ICG NIR fluorescence imaging was performed in 36 patients pre- and post-intervention. Patient characteristics are depicted in Table 1. Revascularization was successful in 32 patients. Of the 36 patients, 21 patients underwent an endovascular revascularization. For the patients undergoing successful revascularization, there was a significant increase in ABI post-revascularization from 0.71 (±0.30) to 0.92 (±0.35) ($p<0.001$) and a significant increase in TP from 59 (±27) to 77 (±18) ($p=0.018$). No significant differences were found in ABI and TP in the control group pre- and post-revascularization (ABI: $p=0.918$, TP: $p=0.137$). No significant changes were seen for the ABI and TP in the four patients in whom revascularization was unsuccessful (ABI: $p=0.895$, TP: $p=0.531$).

Table 1. Patient characteristics.

Patient characteristics (n=36)	Number of patients
Age (years, SD)	70.7 (7.0)
Female	14
Fontaine stage	
2a	4
2b	19
3	9
4	4
Diabetes	12
Hypertension	28
Active smoking	10
Kidney failure	0
Intervention type	
Endovascular	21
Bypass surgery	5
TEA	7
Hybrid	2
Intervention successful	32

NIR fluorescence imaging results

An example of the ICG NIR fluorescence imaging results of a patient pre- and postintervention following a femoro-crural bypass on the left side are displayed in Figure 4 and in supplementary Video 1 (available online via Vascular). The differences as seen on quantitative analyses of the NIR fluorescence intensity in this patient is seen in Figure 5. Collected data of the results for the maximum slope, AUC ingress and AUC egress for the three regions of interests in the revascularized limb group are shown in Table 2. For the maximum slope, a significant increase was seen for all three ROIs. The increase in inflow was most significant for ROI 3, i.e. the hallux (3.7 to 6.6, p=0.000). The AUC ingress showed a significant increase in ROI 3, but no significant difference for ROIs 1 and 2. The AUC egress showed a significant decrease for all three ROIs. This decrease was most significant for ROI 3, i.e. the hallux (49.5 to 42.4, p=0.014). Results pre- and post-intervention were also analyzed for the non-revascularized limb. These results are depicted in Table 3. Besides the AUC ingress for ROI 3, no significant differences were seen for all parameters in all three ROIs.

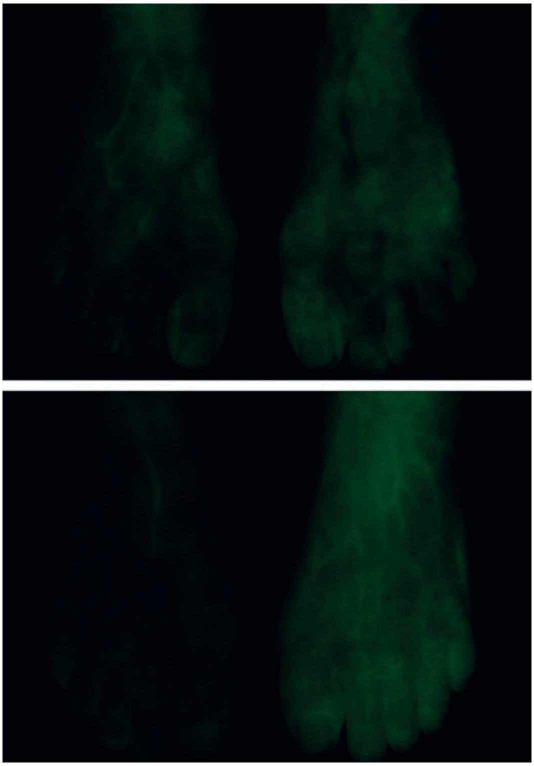

Figure 4. Near-infrared fluorescence intensity before (above) and after (below) bypass surgery on the left side.

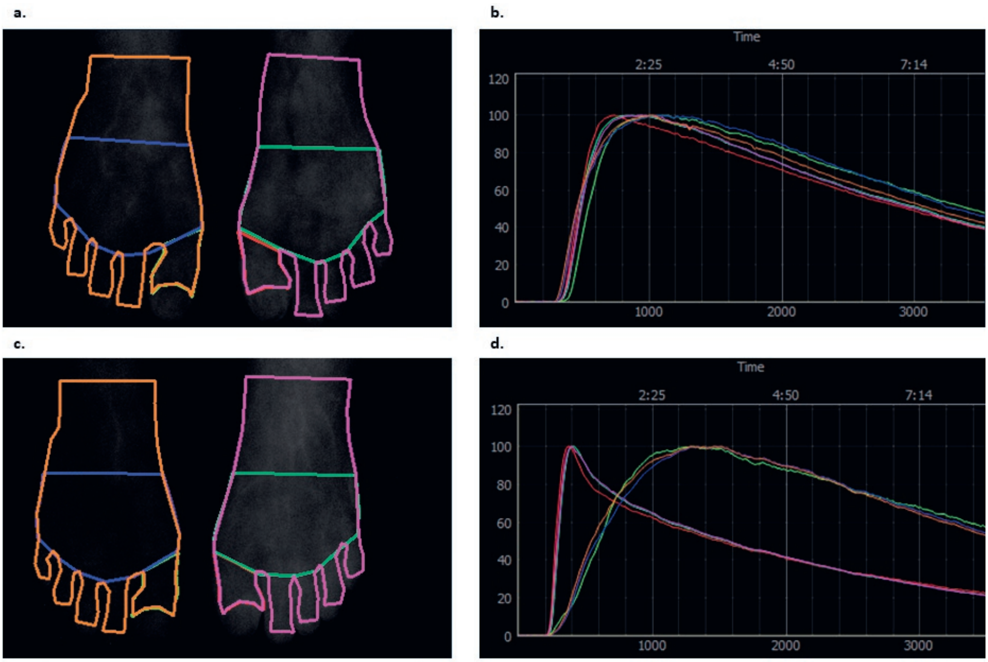

Figure 5. ICG NIR fluorescence imaging results in a patient undergoing femoro-crural bypass surgery on the left side:

a. NIR fluorescence signal and ROI selection pre-revascularization.
b. Normalized time-intensity curves pre-revascularization.
c. NIR fluorescence signal and ROI selection post-revascularization.
d. Normalized time-intensity curves post-revascularization.

Table 2. ICG NIR fluorescence imaging results pre- and post-revascularization in revascularized limb.

Perfusion parameter	**ROI 1**			**ROI 2**			**ROI 3**		
	Pre	Post	p	Pre	Post	p	Pre	Post	p
Maximum slope (%/s)	3.3 ± 2.0	5.6 ± 2.7	0.000	3.4 ± 2.1	5.6 ± 2.5	0.000	3.7 ± 2.2	6.6 ± 3.2	0.000
AUC ingress (%)	70.2 ± 6.3	67.9 ± 8.9	0.681	69.9 ± 6.2	66.2 ± 9.7	0.191	70.6 ± 6.3	64.0 ± 9.7	0.003
AUC egress (%)	52.6 ± 7.2	47.2 ± 9.1	0.004	52.2 ± 8.4	46.8 ± 9.3	0.002	49.2 ± 8.7	41.6 ± 9.8	0.007

Table 3. ICG NIR fluorescence imaging results pre- and post-revascularization in control group.

Perfusion parameter	ROI 1			ROI 2			ROI 3		
	Pre	Post	p	Pre	Post	p	Pre	Post	p
Maximum slope (%/s)	3.2 ± 1.9	3.6 ± 2.3	0.390	3.2 ± 1.9	3.5 ± 2.3	0.304	3.9 ± 2.4	4.6 ± 3.0	0.204
AUC ingress (%)	71.4 ± 5.1	70.4 ± 5.5	0.525	71.2 ± 5.6	69.4 ± 5.0	0.270	70.4 ± 5.5	66.3 ± 7.6	0.029
AUC egress (%)	53.1 ± 5.9	52.4 ± 7.2	0.695	52.4 ± 6.1	52.1 ± 6.8	0.922	50.1 ± 8.2	47.7 ± 9.1	0.501

The four patients for whom revascularization was unsuccessful all underwent endovascular procedures. No significant differences were seen for all three parameters in all three ROIs for both limbs.

Discussion

Currently, the medical field lacks a valid and reliable tool for quantification of changes in tissue perfusion following revascularization. This study emphasizes the potential of ICG NIR fluorescence imaging to fill this gap by showing a significant improvement for 2 out of the 3 parameters in patients undergoing a successful revascularization. No significant differences were seen for these parameters pre- and postintervention in patients with an unsuccessful revascularization, underlining the repeatability of ICG NIR fluorescence imaging for measurement of tissue perfusion. As opposed to the findings reported by Nakamura et al.(13), this study reported no changes for most parameters measured in the contralateral non-treated leg. Although there was a significant increase in AUC ingress in one region in the control group, it is unclear whether this parameter is reliable enough to report changes in foot perfusion. This is emphasized by the non-significant differences found for this parameter in the treated leg. A possible explanation for this finding is the fact that a faster increase will not automatically lead to a higher AUC. Earlier studies on the use of ICG NIR fluorescence imaging in patients with LEAD have shown that significant improvement following revascularization is most often seen in time-related parameters (14). This might be due to the variation in absolute fluorescence intensity, which is influenced by several factors, including camera distance and patient-related factors, such as edema and skin temperature (15). To minimize the effect of these influencing factors, the intensity can be described as a percentage of the measured maximum intensity. The use of this normalization for maximum intensity was used by Kang et al., a study in which perfusion using ICG NIR fluorescence imaging was used in hindlimbs of mice (16). This is the first study to use this approach for analysis in clinical patients with LEAD and in the search for quantitative analysis of tissue perfusion, the use of these normalized parameters seems to be superior to intensity related parameters (17).

The three parameters used in this study were selected following a thorough examination of the time-intensity curves following successful revascularization. Most often, a faster inflow was seen followed by a sharper decline in intensity. To quantify these findings, the parameters were set at maximum slope, AUC ingress and AUC egress. The findings in this study show that the slope and AUC egress have the best potential in future studies on assessment of tissue perfusion with ICG NIR fluorescence imaging following revascularization. These studies should also incorporate data on clinical outcome, which is a limitation of this study. The predictive value of ICG NIR fluorescence imaging on clinical outcome following revascularization was reported earlier in a study by Colvard et al. (18). In this study, an increase in inflow- as well as outflow parameters was found in patients with a clinically successful outcome. Similar to this study, these measurements were performed postinterventional. For the intra-operative guidance of revascularization strategies, studies on the feasibility of the intra-operative use of this technique have to be performed. Furthermore, this study is limited by the heterogeneity and size of the study population. A larger cohort with information about follow-up will lead to better understanding of perfusion patterns and to what extent a patient will benefit from a revascularization procedure. This cohort should also include an analysis on the effect of impaired microcirculation on results found with ICG NIR fluorescence imaging. Earlier studies have reported contradictory results on the in- and outflow patterns between patients with- and without microvascular disease (19, 20). To provide cut-off values to guide treatment strategies, these differences in patient characteristics have to be incorporated.

Conclusion

This study shows the potential of ICG NIR fluorescence imaging in assessing changes in foot perfusion following successful revascularization. The perfusion of the non-treated leg does not appear to be influenced by a revascularization procedure on the contralateral side. Future studies should incorporate normalized parameters and focus on the potential of intra-operative ICG NIR fluorescence imaging in predicting favorable outcome following revascularization.

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