Near-infrared fluorescence imaging with indocyanine green in vascular surgery

Hoven, P. van den

Part III

Summary, discussion and appendices

Chapter 9

Summary

Discussion and future perspectives

Summary

For the assessment of skin circulation in patients with lower extremity arterial disease (LEAD), vascular surgeons rely on physical examination, supported by diagnostic methods providing information about the macrovascular status of the leg. Amongst these methods are the ankle-brachial index, toe pressure measurement and duplex ultrasonography. However, the field of vascular surgery lacks a diagnostic tool for the valid and reliable quantification of tissue perfusion. Near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) is currently used for assessment of tissue perfusion in other surgical fields and could possibly have huge potential in patients with LEAD. This is outlined in **Chapter 1**. With the aim to move the field of vascular surgery forward, this thesis describes the quest for valid and reliable quantitative assessment of skin perfusion using NIR fluorescence imaging with ICG, predominantly in patients with LEAD.

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

This part provides an overview of the past use of ICG NIR fluorescence imaging in tissue perfusion assessment by means of two systematic reviews. Furthermore, the quantification of skin perfusion is explored in three clinical studies of patients with LEAD and patients undergoing reconstructive breast surgery. **Chapter 2** describes a systematic review on the use of ICG NIR fluorescence imaging in patients with peripheral artery disease, more specifically LEAD. This technique was used in these patients for either diagnosis, quality control following revascularization, assessment of tissue viability and angiography. Studies were performed in small cohorts and quantitative analyses showed large variety in used – and appropriate parameters for various indications. In diagnosing LEAD, time-related parameters seemed most appropriate, with a sensitivity between 67% and 100%. In describing the difference in perfusion following successful revascularization, both intensity – and time-related parameters improved significantly in most studies. Although these results seem promising, there is a widespread variation amongst measurement settings and quantification methods. This is further emphasized in **Chapter 3**, which describes the application of quantitative perfusion analysis with ICG NIR fluorescence imaging in all surgical fields in a systematic review on perfusion parameters. Quantitative assessment using this technique has been described in various fields including gastro-intestinal surgery, neurosurgery, reconstructive surgery, transplantation surgery and thyroid surgery. In this systematic review, relative – and time-related parameters seemed most useful in adequately describing tissue perfusion. Comparable to the earlier systematic review, measurement protocols differed amongst studies, including camera settings and ICG dosage. To provide a first step towards the standardization of quantification of tissue perfusion with ICG NIR fluorescence

imaging using the Quest Spectrum Platform®, three clinical studies were performed, described in Chapter 4 to 6. In **Chapter 4,** the ICG NIR fluorescence perfusion patterns in patients with chronic limb-threatening ischemia (CLTI) were compared to non-LEAD control patients. Following intravenous bolus administration of ICG, the fluorescence intensity in the feet was recorded for 10 minutes. Following quantitative assessment of the fluorescence intensity over time on the dorsum of the foot, an increased inflow of ICG was seen for patients with CLTI. This can possible be explained by damage to the regulatory mechanisms of the microcirculation, arterial stiffness and transcapillary leakage. The reliable quantification of tissue perfusion using ICG NIR fluorescence imaging is further explored in **Chapter 5**, in which normalization of the fluorescence intensity was applied. This analyzing method describes the fluorescence intensity change over time as a percentage of the maximum intensity. This resulted in increased reliability for repeated measurements in patients with LEAD. In non-LEAD control patients, this method resulted in a more homogenous perfusion pattern in the foot. To explore the perfusion patterns displayed with ICG NIR fluorescence imaging in reconstructive breast surgery, quantitative assessment of free flaps was performed in **Chapter 6**. On quantitative assessment, the site with the perforator and regions marked as high fluorescence showed superior inflow compared to regions with low fluorescence. Furthermore, within the 3 minute time frame of ICG NIR fluorescence measurement, no outflow was observed for regions marked as low fluorescence.

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

Two indications for which ICG NIR fluorescence imaging could have huge potential are the effect of revascularization procedures on regional foot perfusion and the assessment of tissue viability in patients with wounds. Therefore, this part describes two clinical studies exploring these indications.

In **Chapter 7**, ICG NIR fluorescence imaging was performed pre- and postprocedural in patients undergoing unilateral revascularization. Quantitative perfusion assessment within three regions of the foot demonstrated a significant improvement of in- and outflow following revascularization in the treated limb. The same parameters showed no difference in the contralateral, non-treated limb. Analysis of the ICG NIR fluorescence parameters in patients where revascularization was unsuccessful displayed no differences. To examine the prediction of tissue viability, **Chapter 8** includes a pilot study of patients undergoing amputation surgery and postprocedural ICG NIR fluorescence imaging. This technique was able to predict postoperative skin necrosis in all four cases. Quantitative assessment of the areas with diminished fluorescence displayed a decreased in- as well as outflow of ICG.

Discussion and future perspectives

Reliable assessment of tissue perfusion can have huge consequences for patient outcome within many surgical fields. Therefore, the search for a technique capable of assessing tissue perfusion has been the subject to multiple studies for various indications (1-10). For patients with lower-extremity arterial disease (LEAD), studies have been performed on transcutaneous oxygen pressure measurement, laser speckle imaging and dynamic volume computed tomography (11-14). Although studies on perfusion assessment in patients with LEAD have provided clinical relevance, including cut-off values for wound healing, no single technique has shown to be capable of perfusion assessment. This thesis explored the possible application of near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) for tissue perfusion assessment, an imaging technique with seemingly appropriate features.

First of all, the past use of ICG NIR fluorescence imaging within various surgical fields and vascular surgery in particular is characterized by a large variety in measurement protocols, including camera type, camera settings and ICG dosage. Concerning the camera type, several systems have been used, limiting comparability of fluorescence parameters between studies (15). Furthermore, the camera settings, including camera distance and angle to the camera, vary amongst studies. It is known that these settings influence the signal and therefore should be standardized in order to allow for reliable comparison (16). Thirdly, variations in ICG dosage influence the measured fluorescence intensity, making comparability even more difficult (17). The two systematic reviews in this thesis underline these factors and encourage the use of standardized protocols for the assessment of tissue perfusion using ICG NIR fluorescence imaging. Furthermore, comparability studies between these camera systems are a vital step towards reliable perfusion assessment.

The three studies in this thesis describing the quantification of tissue perfusion in patients with LEAD have provided interesting insights in perfusion patterns of the foot. First of all, it was demonstrated that patients with chronic limb-threatening ischemia had increased inflow of ICG, compared to non-LEAD control patients. This is in contrast to an earlier study by Igari et al. on perfusion assessment with ICG in healthy control patients (18). However, Terasaki et al. did demonstrate faster inflow in patients with advanced stage LEAD (19). Although the superior inflow in this thesis was significant, there is still a large distribution within each group, precluding fierce statements on cut-off values for adequate perfusion. Possibly contributing to this distribution is the high presence of patients with diabetes mellitus, a group often presenting with microvascular – rather than macrovascular disease. Therefore, future studies on perfusion patterns should take this subgroup into account.

To minimize the effect of influencing factors in the measured fluorescence intensity, this thesis describes the application of normalization of time-intensity curves. This was described earlier in studies on gastro-intestinal perfusion (5, 20, 21). It was hypothesized that describing the fluorescence intensity as a percentual change of the maximum intensity, this would enhance the validity and reliability. Concerning repeatability, this method indeed provided good comparability between repeated measurements on the non-treated side of patients undergoing unilateral revascularization. Furthermore, normalized time-intensity curves were comparable amongst various regions of the foot in non-LEAD control patients, in contrary to absolute time-intensity curves. Although normalization enhances the validity and reliability, intensity-related parameters are depleted, which could be useful in the assessment of tissue viability, as shown in the study on clinical translation. Furthermore, normalization of time-intensity curves in areas with diminished fluorescence intensity leads to fluttering of the curves, making them non-interpretable. Therefore, applying normalization to time-intensity curves should be considered depending on the indication.

Concerning the clinical implementation, this thesis has provided two fields within vascular surgery in which ICG NIR fluorescence imaging could make an impact. First of all, this technique was able to quantify changes in foot perfusion following successful revascularization. Although these results are encouraging, studies on correlation with clinical outcome have to be performed in order to define clinical relevance. These studies should also incorporate the analysis of angiosome targeted revascularization, a field within vascular surgery that is still subject to debate (22, 23). The possible prediction of favorable outcome following revascularization using ICG NIR fluorescence imaging can provide guidance in choice and timing of treatment. Secondly, this thesis has made a first step towards the prediction of tissue viability following amputation surgery. Patients with LEAD undergoing amputation surgery are at a disturbingly high risk of re-interventions (24). Although this study has shown a rate of 100% in predicting skin necrosis, this study was performed in only a small cohort of patients. Therefore, studies are already designed to perform ICG NIR fluorescence imaging intra-operatively in larger cohorts. A third possible application in clinical practice includes the prediction of ulcer healing. Although the ethiology of ulcers is multifactorial, adequate perfusion is essential. Although ICG NIR fluorescence imaging shows potential in describing foot circulation, cut-off values to predict ulcer healing have yet to be found. The consequences of adequate prediction of ulcer healing on patient outcome as well as healthcare costs would be enormous.

Alongside the future study of ICG NIR fluorescence imaging for perfusion assessment for the aforementioned applications, there are several other imaging modalities with high potential as well. These include hyperspectral imaging, multispectral imaging

and optoacoustic imaging. Optoacoustic imaging for example, has shown significant differences in microvasculature architecture in patients with diabetes compared to healthy volunteers (25). Hyperspectral imaging, which measures the amount of light at several wavelengths within both the visible and near-infrared light spectrum, has proven to distinct patients with- and without lower-extremity arterial disease (26). With the ultimate goal of reliable quantification of tissue perfusion to improve patient outcome, these potential modalities should be examined in future studies as well.

Traversing all recommendations in this thesis for future studies on the reliable assessment of tissue perfusion using ICG NIR fluorescence imaging, is the call for collaboration. Cooperations between surgical disciplines, both national and international, together with experts in the field of perfusion imaging are needed to bridge the current gaps. Besides the impact reliable perfusion assessment can have on patients with LEAD, this technique has the potential to improve the outcome of patients in many other surgical fields as well.

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