Near-infrared fluorescence imaging with indocyanine green in vascular surgery

Hoven, P. van den

Chapter 1

Introduction and thesis outline

Introduction

Throughout history, surgeons are trained to rely on their physical examination to guide decision making. Concerning the assessment of tissue perfusion, a surgeon relies on subjective and sometimes indirect observations, including tissue temperature, color and the presence of pulses. Although these clinical observations are of vital importance, the surgical field lacks a technique for the reliable and quantitative assessment of tissue perfusion. Within the field of vascular surgery, this becomes visible when interpreting skin circulation in patients with lower extremity arterial disease (LEAD). This disease, which is characterized by the presence of atherosclerotic disease of the lower limb, is diagnosed based on a clinical history and examination, combined with diagnostic tests providing information about the macrovascular status (1). The most utilized diagnostic tests include the ankle-brachial index, toe pressure measurement, duplex ultrasound, digital subtraction angiography, computed tomography angiography and magnetic resonance angiography. While these techniques provide valuable information about lower leg circulation, the actual perfusion on skin level remains unknown. This absence of information about skin perfusion seems the presumable cause that none of these techniques have proven predictive value in wound healing, which can be of paramount importance in patients with chronic-limb threatening ischemia (CLTI) due to ischemic wounds (2). The vulnerable patients in this latter group are at high risk of undergoing a major amputation with a substantial risk of concomitant wound healing problems (3). Besides the prediction of wound healing, adequate assessment of skin perfusion in patients with LEAD has the potential to guide revascularization strategies. Although the decision for a revascularization procedure is thoughtful, the lack of information about foot perfusion might provoke aggressive revascularization strategies with undesirable outcomes. Furthermore, adequate assessment of foot perfusion has the ability to prevent unnecessary interventions. In the search for the reliable assessment of skin perfusion, several imaging techniques have been studied (4-6). Transcutaneous oxygen pressure measurement has proven to predict healing problems following lower limb amputation to a certain extent, however, the additional benefit over clinical assessment has not been demonstrated (6). Other techniques examining the evaluation of tissue perfusion include laser-speckle imaging and dynamic volume perfusion computed tomography. For both techniques, significant differences were seen in foot perfusion when comparing results pre- and postrevascularization procedures (5, 7). However, there is still limited evidence on the validity of these techniques in determining the quality of tissue perfusion. A technique gaining popularity for tissue perfusion assessment is near-infrared (NIR) fluorescence imaging using indocyanine green (ICG). NIR fluorescence imaging is a technique to visualize fluorescence in the NIR light spectrum (780 to 1000nm). A NIR fluorescence imaging system consists of a light engine, exciting the target tissue, combined with a camera measuring the fluorescence intensity (Figure 1). The advantages of fluorescence imaging in the NIR spectrum over visible light include the relatively deep tissue penetration of up to one centimeter and the low effect of autofluorescence (8). These features enable the system to clearly visualize a fluorophore with an excitation – and emission peak in the NIR light spectrum. The most utilized fluorophore for the assessment of tissue perfusion in near-infrared fluorescence imaging is ICG. This negatively charged, ambiphilic, water soluble tricarbocyanine was approved by the Food and Drug Administration in 1957 and has very low toxicity and side effects (9, 10). The feasibility of ICG for assessment of perfusion is explained by several properties. First of all, ICG has excellent fluorescence properties for NIR fluorescence imaging, with an excitation peak of 780nm and an emission peak of 820nm (11). Secondly, upon intravenous administration, ICG binds to plasma proteins, confining the fluorophore to the intravascular compartment (11). Furthermore, ICG has a rapid hepatic clearance, minimizing interference with the registered fluorescence intensity over time in the target tissue (12). The first reported use of this technique for assessment of vascular anatomy was in the field of ophthalmology (13). Since then, ICG in NIR fluorescence imaging has been performed in various surgical fields including gastro-intestinal surgery, cardiac surgery, and reconstructive surgery (14-19). Within the field of vascular surgery, perfusion assessment using ICG NIR fluorescence imaging has been used for various indications, including diagnosis of LEAD, quality control following revascularization and for assessment of tissue viability following amputation surgery (20-22). Following ICG NIR fluorescence imaging of the target area or so called region of interest (ROI), skin perfusion analysis is performed by either a qualitative or quantitative analysis. For qualitative analysis, this means the perfusion is interpreted based on subjective evaluations of the fluorescence intensity by the observer. For a quantitative analysis, the fluorescence intensity is most often expressed in arbitrary units (a.u.). Furthermore, the fluorescence intensity can be analyzed by creating time-intensity curves, describing the fluorescence intensity change over time. Both qualitative and quantitative analyses of ICG NIR fluorescence imaging in assessment of skin perfusion for patients with LEAD have been performed and have shown varying results (23-25). This can partially be attributed to the differences in used camera systems and used quantification software. Besides, these studies varied among design and were mostly performed in an experimental pilot setting. Furthermore, the interpretation of the fluorescence intensity can be misleading, as the signal is influenced by several factors, including camera distance and angle to the target tissue (26). In the quest towards reliable perfusion assessment with ICG NIR fluorescence imaging, these challenges have to be overcome. Therefore, this thesis aims to further assess the value of ICG NIR fluorescence imaging for perfusion assessment in vascular surgery and explore potential applications for use in clinical practice.

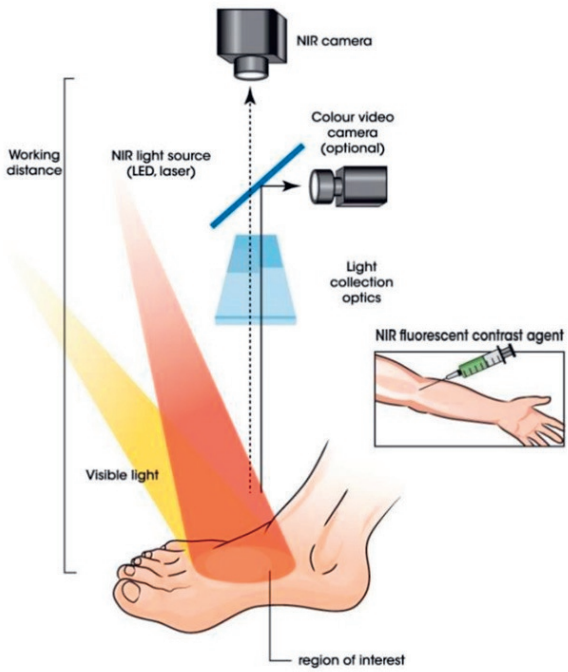

Figure 1. ICG NIR fluorescence imaging setup.

Reference list

1. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55(3):305-68.
2. 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(12):e657-e72.
3. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Disease Burden and Clinical Outcomes Following Initial Diagnosis of Critical Limb Ischemia in the Medicare Population. JACC Cardiovasc Interv. 2018;11(10):1011-2.
4. Benitez E, Sumpio BJ, Chin J, Sumpio BE. Contemporary assessment of foot perfusion in patients with critical limb ischemia. Semin Vasc Surg. 2014;27(1):3-15.
5. Cindil E, Erbas G, Akkan K, Cerit MN, Sendur HN, Zor MH, et al. Dynamic Volume Perfusion CT of the Foot in Critical Limb Ischemia: Response to Percutaneous Revascularization. AJR Am J Roentgenol. 2020;214(6):1398-408.
6. Arsenault KA, Al-Otaibi A, Devereaux PJ, Thorlund K, Tittley JG, Whitlock RP. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2012;43(3):329-36.
7. Kikuchi S, Miyake K, Tada Y, Uchida D, Koya A, Saito Y, et al. Laser speckle flowgraphy can also be used to show dynamic changes in the blood flow of the skin of the foot after surgical revascularization. Vascular. 2019;27(3):242-51.
8. Frangioni JV. In vivo near-infrared fluorescence imaging. Curr Opin Chem Biol. 2003;7(5):626-34.
9. Fox IJ, Brooker LG, Heseltine DW, Essex HE, Wood EH. A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. Proc Staff Meet Mayo Clin. 1957;32(18):478-84.
10. Obana A, Miki T, Hayashi K, Takeda M, Kawamura A, Mutoh T, et al. Survey of complications of indocyanine green angiography in Japan. Am J Ophthalmol. 1994;118(6):749-53.
11. Landsman ML, Kwant G, Mook GA, Zijlstra WG. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. J Appl Physiol. 1976;40(4):575-83.
12. Alander JT, Kaartinen I, Laakso A, Patila T, Spillmann T, Tuchin VV, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging. 2012;2012:940585.
13. Kogure K, Choromokos E. Infrared absorption angiography. J Appl Physiol. 1969;26(1):154-7.
14. Vahrmeijer AL, Hutteman M, van der Vorst JR, van de Velde CJ, Frangioni JV. Image-guided cancer surgery using near-infrared fluorescence. Nat Rev Clin Oncol. 2013;10(9):507-18.
15. Schaafsma BE, Mieog JS, Hutteman M, van der Vorst JR, Kuppen PJ, Lowik CW, et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. J Surg Oncol. 2011;104(3):323-32.

16. Yamamoto M, Nishimori H, Handa T, Fukutomi T, Kihara K, Tashiro M, et al. Quantitative assessment technique of HyperEye medical system angiography for coronary artery bypass grafting. Surg Today. 2017;47(2):210-7.
17. Detter C, Russ D, Iffland A, Wipper S, Schurr MO, Reichenspurner H, et al. Near-infrared fluorescence coronary angiography: a new noninvasive technology for intraoperative graft patency control. Heart Surg Forum. 2002;5(4):364-9.
18. Munabi NC, Olorunnipa OB, Goltsman D, Rohde CH, Ascherman JA. The ability of intra-operative perfusion mapping with laser-assisted indocyanine green angiography to predict mastectomy flap necrosis in breast reconstruction: a prospective trial. J Plast Reconstr Aesthet Surg. 2014;67(4):449-55.
19. Driessen C, Arnardottir TH, Lorenzo AR, Mani MR. How should indocyanine green dye angiography be assessed to best predict mastectomy skin flap necrosis? A systematic review. J Plast Reconstr Aesthet Surg. 2020;73(6):1031-42.
20. Terasaki H, Inoue Y, Sugano N, Jibiki M, Kudo T, Lepantalo M, et al. A quantitative method for evaluating local perfusion using indocyanine green fluorescence imaging. Ann Vasc Surg. 2013;27(8):1154-61.
21. 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(7):1919-26.
22. Yang AE, Hartranft CA, Reiss A, Holden CR. Improving Outcomes for Lower Extremity Amputations Using Intraoperative Fluorescent Angiography to Predict Flap Viability. Vasc Endovascular Surg. 2018;52(1):16-21.
23. Zimmermann A, Roenneberg C, Wendorff H, Holzbach T, Giunta RE, Eckstein HH. Early postoperative detection of tissue necrosis in amputation stumps with indocyanine green fluorescence angiography. Vasc Endovascular Surg. 2010;44(4):269-73.
24. Igari K, Kudo T, Uchiyama H, Toyofuku T, Inoue Y. Indocyanine green angiography for the diagnosis of peripheral arterial disease with isolated infrapopliteal lesions. Ann Vasc Surg. 2014;28(6):1479-84.
25. Colvard B, Itoga NK, Hitchner E, Sun Q, Long B, Lee G, et al. SPY technology as an adjunctive measure for lower extremity perfusion. J Vasc Surg. 2016;64(1):195-201.
26. Pruimboom T, van Kuijk SMJ, Qiu SS, van den Bos J, Wieringa FP, van der Hulst R, et al. Optimizing Indocyanine Green Fluorescence Angiography in Reconstructive Flap Surgery: A Systematic Review and Ex Vivo Experiments. Surg Innov. 2020;27(1):103-19.

Thesis outline

This thesis is divided in three parts, preceded by the introduction in **Chapter 1**. **Part I** focuses on the quantification of tissue perfusion using ICG NIR fluorescence imaging. In **Part II**, the clinical applications of quantitative ICG NIR fluorescence imaging for the assessment of tissue perfusion are explored. **Part III** includes the summary, discussion and appendices of this thesis.

Part I

This section starts with a systematic review about the use of ICG NIR fluorescence imaging in patients with LEAD, displayed in **Chapter 2**. To provide an overview of the wide variety of performed quantification methods in ICG NIR fluorescence imaging, **Chapter 3** describes a systematic review about the parameters used for quantification of tissue perfusion in various surgical fields. In the three chapters following these systematic reviews, the quantification of tissue perfusion is assessed in original articles. **Chapter 4** provides an overview of the ICG NIR fluorescence perfusion patterns of CLTI patients compared to non-LEAD control patients. In **Chapter 5**, the effect of normalization on the measured fluorescence time-intensity curves is displayed. The quantification of free flap tissue perfusion using ICG NIR fluorescence during reconstructive breast surgery is demonstrated in **Chapter 6**.

Part II

This part evaluates the potential clinical applications of quantitative ICG NIR fluorescence imaging in vascular surgery. **Chapter 7** demonstrates the reliability of ICG NIR fluorescence imaging to assess changes in tissue perfusion following revascularization procedures. The predictive value of quantitative ICG NIR fluorescence imaging is shown in **Chapter 8**, which comprises the use of this technique in predicting tissue viability following amputation surgery.

Part III

The summary of the thesis and general discussion with future perspectives on the use of ICG NIR fluorescence imaging in vascular surgery as well as other surgical disciplines are pointed out in **Chapter 9**. Finally, the Dutch summary, curriculum vitae and list of publications of the author are shown in **Chapter 10**.