Near-infrared fluorescence imaging with indocyanine green in vascular surgery
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Chapter 6

Quantification of near-infrared fluorescence imaging with indocyanine green in free flap breast reconstruction

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Abstract

Introduction

One of the complications of free flap breast reconstruction is the occurrence of skin - and fat necrosis. Intra-operative use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has the potential to predict these complications. In this study, quantification of the fluorescence intensity measured in free flap breast reconstruction was performed to gain insight in the perfusion patterns observed with ICG NIR fluorescence imaging.

Methods

ICG NIR fluorescence imaging was performed in patients undergoing free flap breast reconstruction following mastectomy. After completion of the arterial and venous anastomosis, 7.5mg ICG was administered intravenously. The fluorescence intensity over time was recorded using the Quest Spectrum platform®. Four regions of interest (ROI) were selected based on location and interpretation of the NIR fluorescence signal: 1. The perforator, 2. Normal perfusion, 3. Questionable perfusion and 4. Low perfusion. Time-intensity curves were analyzed and two parameters were extracted: Tmax and Tmax slope.

Results

Successful ICG NIR fluorescence imaging was performed in 13 patients undergoing 17 free flap procedures. Region selection included 16 perforator -, 17 normal perfusion -, 8 questionable perfusion - and 5 low perfusion ROIs. Time-intensity curves of the perforator ROIs were comparable to the ROIs of normal perfusion and demonstrated a fast inflow. No outflow was observed for the ROIs with questionable and low perfusion.

Conclusion

This study provides insight in the perfusion patterns observed with ICG NIR fluorescence imaging in free flap breast reconstruction. Future studies should correlate quantitative parameters with clinical perfusion assessment and outcome.

Introduction

Breast cancer accounts for 30 percent of newly diagnosed malignancies in female patients and it is the leading cause of death among middle-aged women (1). The surgical treatment of breast cancer is performed either with breast-conserving surgery or mastectomy. For reconstructive surgery following mastectomy, the use of autologous tissue is gaining popularity (2). Commonly performed autologous breast reconstruction procedures include deep inferior epigastric artery perforator (DIEP) -, superficial inferior epigastric artery (SIEA) - and profunda artery perforator (PAP) flap reconstructions (3, 4). The advantages of successful autologous breast reconstruction, including long-term beneficial outcome, are evident. However, free flap surgery following mastectomy is also associated with complications including skin – and fat necrosis (5, 6). In the assessment of tissue perfusion during free flap surgery, the surgeon relies on subjective observations including skin color, capillary refill and the occurrence of bleeding. Possible techniques to aid the surgeon while assessing tissue perfusion include laser doppler and near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) (7). ICG NIR fluorescence imaging is a technique that measures fluorescence in the NIR light spectrum (700-900nm), which is characterized by deep tissue penetration and low autofluorescence (8). Following intravenous administration of ICG, a fluorophore with an absorption and excitation peak in the NIR light spectrum, a time-intensity curve of the measured fluorescence intensity can be generated. The feasibility of ICG in perfusion assessment is explained by its confinement to the vascular component due to binding with serum proteins including albumin (9). For patients undergoing breast (reconstructive) surgery, the intra-operative use of ICG NIR fluorescence imaging was demonstrated to aid surgeons in their assessment of skin viability, thereby reducing the occurrence of skin necrosis in several studies (10, 11). This reduction in necrosis can be explained by the intra-operative removal of tissue with diminished fluorescence intensity observed with ICG NIR fluorescence imaging. The localization of areas with diminished perfusion is based on subjective evaluation of the measured fluorescence intensity by the surgeon (12). However, to objectively assess tissue perfusion and enhance the reliability of this technique, quantification of the fluorescence intensity is of paramount importance. Quantification studies on the use of ICG NIR fluorescence imaging in reconstructive surgery mainly have focused on absolute and relative fluorescence intensity parameters (10, 13, 14). However, there is no consensus on which parameter is most accurate for the assessment of tissue perfusion. In the search for determining cut-off values for tissue perfusion, more information is needed about the perfusion patterns observed with ICG NIR fluorescence imaging. Therefore, the aim of this study was to gain insight in these perfusion patterns by performing quantitative assessment of the ICG NIR fluorescence imaging used in free flap breast reconstruction.

Methods

This pilot cohort study was approved by the Medical Research and Ethics Committee of the Leiden University Medical Center and was conducted in accordance with the Declaration of Helsinki. Patients undergoing autologous breast reconstruction between February - and September 2019 in a single tertiary hospital in the Netherlands were included. Exclusion criteria were allergy to ICG, iodine or shellfish and impaired renal function. This study adhered to the STROBE statement on the report of cohort studies (15).

ICG NIR fluorescence imaging measurement

Intra-operative ICG NIR fluorescence imaging was performed using the Quest Spectrum Platform® (Quest Medical Imaging, Middenmeer, The Netherlands). This camera system consists of a laser with a camera that measures light in the visible and NIR light spectrum (700-830nm). Directly following an intravenous bolus injection of 7.5 mg ICG (VERDYE 25 mg, Diagnostic Green GmbH, Aschheim-Dornach, Germany), the fluorescence intensity of the anastomosed free flap was recorded for 3 minutes according to protocol. The perforator, including artery and vein, was marked with a staple. Measurements were performed with the camera placed perpendicular to the flap surface at a distance of approximately 50 centimeters. The operating room was cleared of ambient light throughout the measurement.

Data analysis

Postoperatively, a reconstructive surgeon (PV) evaluated the fluorescence intensity videos and, if observed, selected four regions of interest (ROI): 1. Perforator, 2. Normal perfusion, 3. Questionable perfusion (possible resection) and 4. Low perfusion (resection). The selected ROIs were analyzed using the Quest Research Framework® (Quest Medical Imaging, Middenmeer, the Netherlands). For the selected ROIs, the software creates a time-intensity curve of the measured intensity in arbitrary units (a.u.). Videos were analyzed for 3 minutes following start of intensity increase. Two parameters were extracted (Figure 1): time to maximum intensity (Tmax) and time to maximum slope (Tmax slope). Baseline subtraction was applied to all time-intensity curves. A tracker synchronized the ROI with movement. Videos without data on camera settings were excluded. Statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.). Results for the four ROIs were compared using the Kruskal-Wallis test.

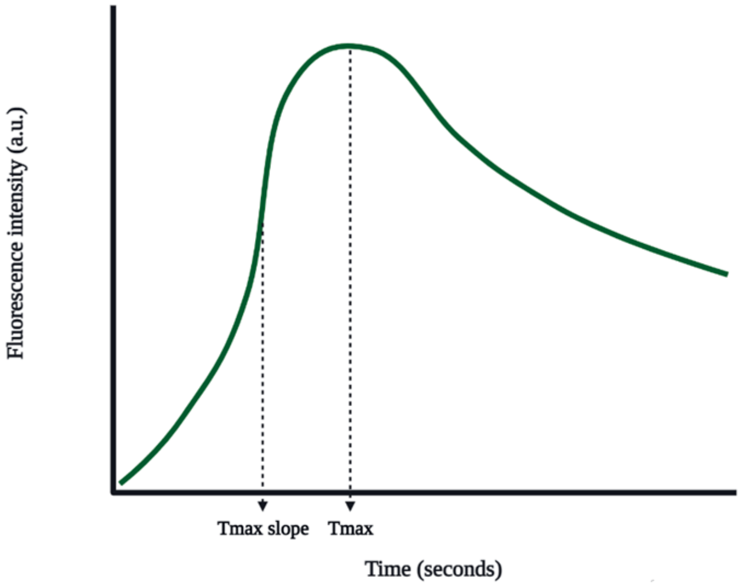

Figure 1. Time-intensity curve with extracted parameters.

Results

Successful ICG NIR fluorescence imaging was performed in 13 patients undergoing 13 DIEP -. 3 PAP - and 1 SIEA flap reconstruction(s). Four patients underwent a bilateral free flap reconstruction. The patient characteristics are displayed in Table I. An example of a normal perfusion pattern is shown in Figure 2 and Video 1 (available online via JPRAS), in which the fluorescence intensity change over time in a 65-year old patient undergoing a DIEP flap reconstruction is displayed. The video is accelerated elevenfold and demonstrates the NIR fluorescence intensity change during the measurement of 3 minutes. An example of a normal and questionably perfused ROI in a 55-year old patient following DIEP flap surgery is shown in Figure 3. The ROI selection included 16 perforator -, 17 normal perfusion -, 8 questionable perfusion - and 5 low perfusion areas. In one patient undergoing a DIEP flap reconstruction, 2 perforators were used.

Table I. Patient characteristics.

Characteristics	Number of patients (n=13)
Age (years, SD)	50.4 (10.6)
Diabetes	0
Hypertension	2
Active smoking	1
Type reconstructive surgery	
DIEP	10
PAP	2
SIEAP	1

Abbreviations: SD, standard deviation; DIEP, deep inferior epigastric perforator; PAP, profunda artery perforator; SIEAP, superficial inferior epigastric artery perforator.

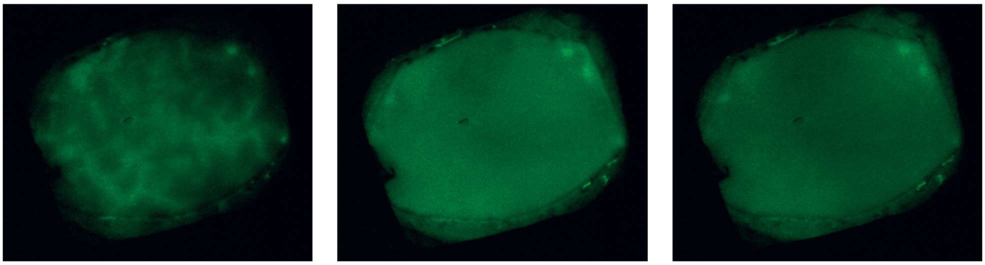

Figure 2. NIR fluorescence intensity change over time in a patient undergoing a DIEP flap reconstruction.

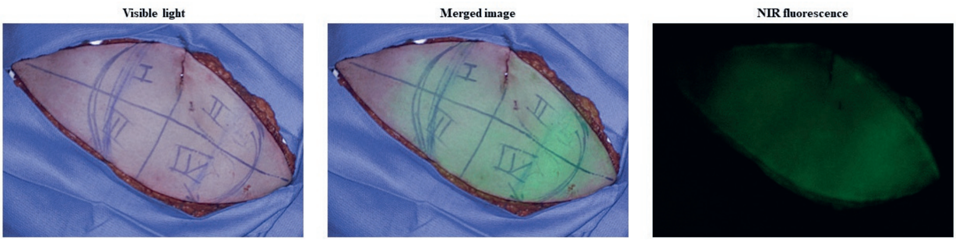

Figure 3. ICG NIR fluorescence imaging in a patient undergoing a DIEP flap reconstruction showing the visible (left), merged (middle) and NIR fluorescence (right) output.

Time-intensity curves

The time-intensity curves for the four selected ROIs are shown in Figure 4. For the perforator ROI, the majority of curves display a steep ingress followed by a steep egress. The egress phase is reached within 180 seconds for all time-intensity curves in this ROI. For the time-intensity curves in the ROIs marked as normal perfusion, an inflow pattern similar to the perforator ROI can be observed. Furthermore, comparable to the perforator ROI, the egress phase is reached within 180 seconds in the majority of ROIs with normal perfusion. For both ROIs, there is a widespread distribution among measured maximum fluorescence intensity between curves. For the ROIs with questionable and low perfusion, a clearly lower maximum fluorescence intensity is demonstrated compared to the perforator and normal perfusion ROIs. Moreover, the curves for questionable and low perfusion ROIs are characterized by a prolonged inflow and the egress phase is not reached for all time-intensity curves in these ROIs.

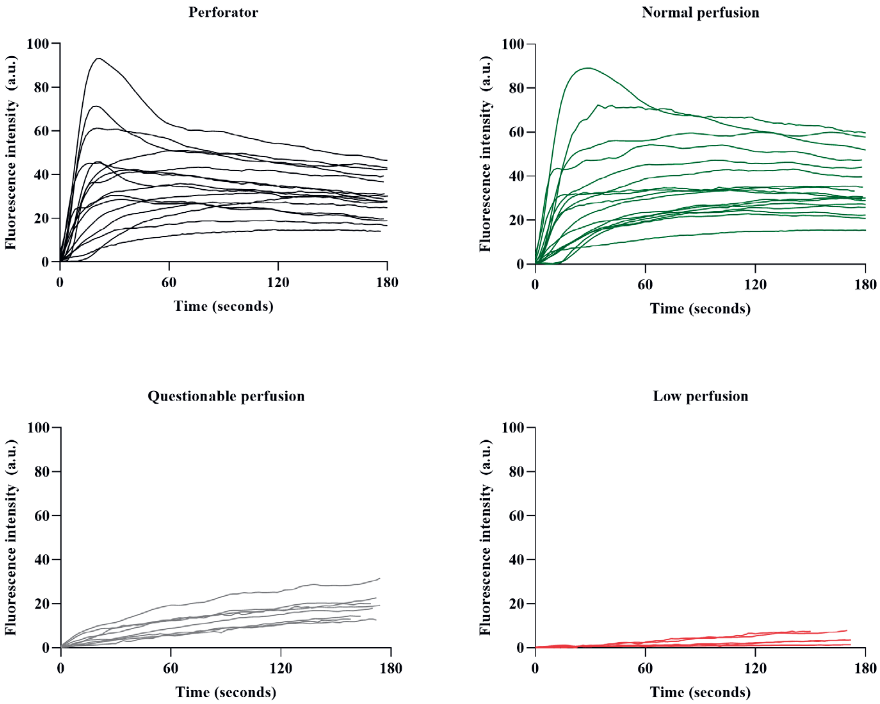

Figure 4. Time-intensity curves for the four measured ROIs.

Quantitative analysis

The results on quantitative analysis of the time-intensity curves for the four ROIs are depicted in Table II and Figure 5. The Tmax was reached earliest in the perforator ROI (63.9 seconds, standard deviation 47.8). For the Tmax slope, results between the perforator – and normal perfusion ROIs were similar 7.2 and 6.8 seconds). Tmax and Tmax slope were prolonged in the ROI with low perfusion (164.9 and 99.1 seconds respectively). Differences between the ROIs were statistically significant for both parameters (Tmax: $p<0.001$, Tmax slope: $p=0.006$).

Table II. Quantitative analysis of the time-intensity curves displaying the Tmax and Tmax slope for each ROI.

	Perforator artery	Normal perfusion	Questionable perfusion	Low perfusion
Tmax, seconds (SD)	68.6 (49.5)	111.3 (42.2)	159.9 (12.7)	164.9 (30.4)
Tmax slope, seconds (SD)	5.6 (3.8)	4.7 (3.1)	20.2 (27.4)	83.9 (18.1)

Abbreviations: SD, standard deviation.

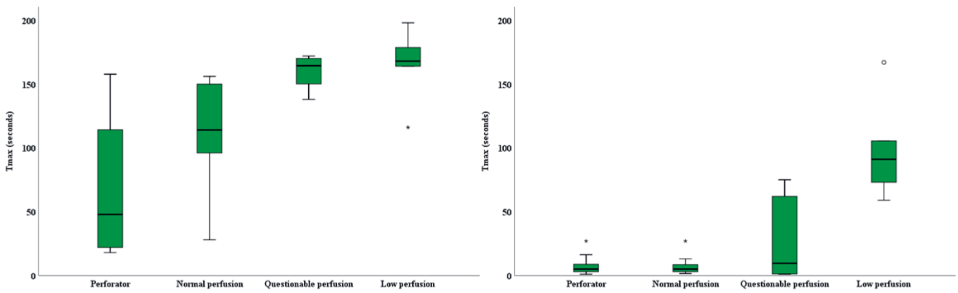

Figure 5. Quantitative analysis of the four ROIs showing the Tmax (left) and Tmax slope (right).

Clinical outcome and follow-up

Flap loss occurred in one patient undergoing a bilateral DIEP flap reconstruction. In this 44-year old female, the DIEP flap on the right side had to be removed, after a failed salvage procedure, on the fourth day postoperatively due to venous congestion. No low - or questionable perfusion ROIs were observed with ICG NIR fluorescence imaging intra-operatively.

Discussion

This study on the quantitative evaluation of ICG NIR fluorescence imaging in free flap breast reconstruction provides insight in the perfusion patterns of free flaps as observed by the surgeon. Interestingly, time-intensity curves for the perforator region were comparable to the regions classified as normal perfusion. Furthermore, these are the only observed regions in which outflow was observed. Current use of ICG NIR fluorescence imaging in free flap breast reconstruction relies on the qualitative and therefore subjective judgement of the NIR signal by the surgeon. However, to aid in decision making and enhance the reliability of ICG NIR fluorescence imaging in these patients, quantitative analysis is required. For quantitative assessment of tissue perfusion in breast surgery, studies on mastectomy skin flap necrosis have shown relative perfusion deficits to be predictive of tissue necrosis (16-18). Relative parameters are described as a percentage of the measured maximum intensity in the target area. For patients undergoing autologous breast reconstruction, relative parameters were used as a cut-off value by Alstrup et al. to guide intra-operative decision-making on the excision of poorly perfused tissue (19). However, this study found no significant differences regarding skin necrosis between patients with - and without the use of ICG NIR fluorescence imaging. Relative parameters are influenced by the measured fluorescence intensity and therefore subjective to various influencing factors including camera angle, camera distance and ICG dosage (13, 20). Moreover, relative intensity parameters provide no data about intensity change over time. For assessment of perfusion in free flaps following microvascular anastomosis, it seems reasonable time-related parameters are more appropriate in predicting in- and outflow. This was observed in a study on the perfusion of fibular free flaps for reconstruction of hemimandibulectomy defects, in which an increased postoperative slope was found following surgical revision due to venous thrombosis (21). Concerning the quantitative analysis of ICG NIR fluorescence imaging in free flap breast reconstruction, one study assessed various perfusion patterns in DIEP flap surgery and found an increased fluorescence intensity as well as the fluorescence intensity inflow rate for perforator regions compared to more distal regions of the flap (22). These results are similar to the findings in this study, in which an increased inflow was observed for the perforator and normal perfusion ROIs. However, in exploring the value of inflow parameters in assessment of perfusion and prediction of clinical outcome, a larger cohort is needed, which is a limitation of this study. Furthermore, only one event of flap loss occurred in this study, precluding evaluation of the predictive value of quantitative assessment of ICG NIR fluorescence imaging for this outcome. Correlating quantitative parameters with clinical assessment and outcome can identify cut-off values for reliable tissue perfusion. Moreover, in this search towards valid an reliable use of ICG NIR fluorescence imaging for perfusion assessment, it is of paramount importance that comparability studies are performed between different camera systems. As shown in a review by Dsouza et al., commercially available ICG NIR fluorescence imaging systems differ in settings, including the excitation source and light sensors (23). Therefore, comparing the perfusion patterns in free flaps measured with various camera systems will provide insight in the applicability of this technique. Despite these limitations, the present study provides insight in the observed perfusion patterns for various regions which is a step towards the quantification of tissue perfusion in free flap surgery. Future studies should focus on the standardization of ICG NIR fluorescence imaging in free flap surgery and correlate quantitative parameters with clinical perfusion assessment and clinical outcome, including fat necrosis and flap viability. When performed in large cohorts, these studies can identify perfusion patterns correlated with these clinical outcomes.

Thise possible early stage prediction of fat necrosis and skin flap viability using ICG NIR fluorescence imaging will have a significant impact on patient outcome.

Conclusion

This study provides insight in the perfusion patterns observed with ICG NIR fluorescence imaging in free flap breast reconstruction. Future studies with this technique in free flap surgery should focus on the correlation of quantitative parameters with clinical perfusion assessment and outcome.

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