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Exploring the clinical applicability of quantitative near-infrared fluorescence imaging with indocyanine green: towards objective and standardized assessment of tissue perfusion

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Citation

Tange, F. P. (2026, September 15). *Exploring the clinical applicability of quantitative near-infrared fluorescence imaging with indocyanine green: towards objective and standardized assessment of tissue perfusion*. Retrieved from <https://hdl.handle.net/1887/4309589>

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Note: To cite this publication please use the final published version (if applicable).

Chapter 7





Establishing reference curves for vital tissue perfusion using quantitative near-infrared fluorescence imaging with indocyanine green

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Published in Langenbeck's Archives of Surgery, January 2025.

Abstract

Purpose

Assessment of tissue perfusion using near-infrared fluorescence (NIR) with indocyanine green (ICG) is gaining popularity, however reliable and objective interpretation remains a challenge. Therefore, this study aimed to establish reference curves for vital tissue perfusion across target tissues using this imaging modality.

Methods

Data from five prospective study cohorts conducted in three Dutch academic medical centres between December 2018 and June 2023 was included. Quantitative analysis using time-intensity curves was performed in ten target tissues, including the colon, ileum, gastric conduit, deep inferior epigastric artery perforator (DIEP) flap, skin of the foot, trachea, sternocleidomastoid muscle (SCM), carotid artery, parathyroid gland, and skin of the neck.

Results

A total of 178 patients were included in this study, representing 303 target tissues. Three different patterns of reference curves were identified based on a subjective assessment. Seven out of ten tissues showed a reference curve with rapid inflow (median time-to-max (tmax): 13.0–17.8 s, median maximum-normalized-slope (slope norm): 10.6–12.6%/sec), short outflow (median area-under-the-curve of tmax + 60 s (AUC60): 65.0–85.1%) followed by a gradual/absent outflow. Secondly, the DIEP flap and SCM tissue showed a reference curve with longer inflow (median tmax: 24.0, 22.0 s, median slope norm: 9.3, 9.7%/sec respectively) and reduced outflow (median AUC60: 89.1, 89.0% respectively). Thirdly, the skin of the foot showed slow inflow (median tmax 141.1 s, median norm slope 2.1%/sec) without outflow.

Conclusion

This study demonstrates reference curves for vital tissue perfusion of multiple target tissues identified with ICG NIR fluorescence imaging, providing a critical step towards the clinical implementation of this technique.

Introduction

Adequate assessment of tissue perfusion is a critical part of surgery and heavily influences patient outcomes.^{1–4} Compromised tissue perfusion can lead to severe complications such as impaired wound healing, necrosis, and organ dysfunction.^{5–11} Traditionally, tissue perfusion assessment has predominantly relied on clinical judgement including visual inspection, palpation, and tissue temperature. While clinical judgement remains indispensable in surgical decision-making, it is a subjective method that often lacks predictive accuracy.^{12–14} Moreover, surgical procedures are increasingly performed minimally invasive, impeding adequate assessment.¹⁵ To reduce the risk of undesired outcomes related to malperfusion, the implementation of a more objective modality for perioperative perfusion assessment can offer significant clinical value.^{5, 16, 17} One of these modalities is near-infrared (NIR) fluorescence imaging with indocyanine green (ICG), a valuable technique that is already being used extensively in various surgical fields.^{9, 17–25} This technique uses the contrast dye ICG which can be visualised by a NIR camera system upon intravenous injection, allowing real-time perfusion assessment. This imaging modality has been widely evaluated in the literature, including large, randomized trials, often by using a qualitative and therefore subjective interpretation of the fluorescence signal.^{26–28} In recent years, studies focusing on quantification of the fluorescence intensity are emerging, supported by the increasing availability of dedicated software programs for this purpose. For various target tissues, these studies have shown that quantification of the fluorescence significantly improves the validity and reliability of ICG NIR fluorescence imaging.^{22, 24, 29–31} However, the high variability of utilized quantification methods impedes the clinical usefulness and hampers adequate interpretation of actual perfusion.^{24, 32} The results however always focus on the interpretation of time-intensity curves. Moreover, it is essential to establish reference curves of perfusion for vital tissue. These reference curves could serve as a threshold for the differentiation between adequately and inadequately perfused tissue.^{20, 22, 24, 29, 30, 33} As an initial step, this study aims to explore the reference curves of adequate perfusion in multiple vital target tissues.

Methods

Data originating from five separately designed prospective study cohorts conducted in three Dutch academic centres was pooled. The included tissue types and imaging protocols of each study cohort are described in Table 1. Each study cohort was approved by the respective medical ethics committee and was performed according to the declaration of Helsinki (10th version, Fortaleza, 2013). All patients provided informed consent. Each study cohort used ICG VERDYE (25 mg vial, Diagnostic Green GmbH, Aschheim-Dornach, Germany) which was intravenously injected, directly followed by a saline flush. The fluorescence videos were all recorded with the Quest Spectrum 2.0 camera system (Quest Medical Imaging, Middenmeer, the Netherlands).

Data collection

The data for this study was collected from December 2018 to June 2023. For the colorectal resection and the gastric conduit cohort, the data was acquired according to previously described study protocols.^{29, 30} The data from the DIEP flap cohort originates from an ongoing randomised controlled trial (NCT05507710) and was acquired according to the published trial protocol.³⁴ Data from the skin foot study cohort originates from the control group of a previously published study by van den Hoven et al.¹⁴ The total thyroidectomy cohort is an ongoing study from which the included data was collected (UMCG research register: 201,900,307). The fluorescence imaging was performed directly after the total thyroid gland was resected.

Data analysis

All acquired fluorescence videos were analysed using the Quest Research Framework® software (Quest Medical Imaging, Middenmeer, the Netherlands). An overview of the signal quantification workflow in two example cases is visualized in Fig. 1. The ROIs for this study were systematically defined by the first author for each tissue type to ensure consistency, independent of previously used ROI's of each study cohort. For each tissue, the ROI placement was guided by clinical assessment (expert surgeon opinion) of perfusion adequacy and aimed to capture the most representative regions. If there was uncertainty in the clinical assessment of vitality, tissue ROIs were excluded. In the colon and ileum groups, the ROI was located most distally from the resection plane, or on a visual part of the colon/ileum which was not operated on. The selected ROI of the gastric conduit was located at the most proximal part of the gastric conduit (nearest to the pylorus). The selected DIEP flap ROI directly surrounded the location where the perforator artery entered the flap. The ROI of the skin foot group consisted of the total dorsum of the foot, including the toes. The selected ROI for the skin of the neck group was located dorsal from the incision wound. The selected ROI on the sternocleidomastoid muscle (SCM) was located at the best visual part of the muscle. For the carotid artery, the ROI comprised the total visual artery. The ROI of the trachea was set at the complete visual trachea. In the parathyroid gland group, the included patients did not suffer from postoperative hypoparathyroidism. The parathyroid glands were identified by the attending surgeon and all visual glands were selected as ROIs.

The fluorescence signal from each ROI was quantified into a time-intensity curve, displaying the fluorescence intensity over time. Both absolute and normalized time-intensity curves were generated, and three parameters were calculated from the normalized time-intensity curves, including the time to maximum intensity (Tmax), maximum normalized slope (slope norm) and the area under the curve + 60 s after Tmax (AUC60).

Normalization of the time-intensity curves was performed according to a previously described method.³⁵ Baseline subtraction, motion tracking and a moving average filter were applied in the quantification software. All fluorescence videos were analysed for two minutes. To analyse the perfusion patterns, the curves were subjectively categorized into three distinct patterns based on visual assessment, parameter values and expert judgement.

The Kruskal–Wallis test was employed for an overall comparison of Tmax, Slope norm, and AUC60 values across the three identified perfusion pattern groups. To examine differences between each pair of patterns within the three perfusion parameters, pairwise comparisons were conducted using the Mann–Whitney U-test. A p-value of less than 0.05 was considered statistically significant for all tests. Statistical analysis was performed using IBM SPSS Statistics 29.0 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp).

Table 1. Imaging protocols of study cohorts

Included tissues	Study cohorts	Camera system	Camera distance (cm)	Camera settings (gain/exposure)	ICG dosage	Duration fluorescence recordings (min)
Colon Ileum	Colorectal resection (38)	Quest Spectrum 2.0	30	20.0dB/ 50ms	5mg	5
Gastric conduit	Oesophagectomy – gastric conduit reconstruction (39)	Quest Spectrum 2.0	30	20.0dB/ 100ms	5mg	5
DIEP flap	DIEP flap (41)	Quest Spectrum 2.0	60	21.6dB/ 200ms	7.5mg	2 or 4
Skin foot	Skin foot (15)	Quest Spectrum 2.0	50	20.0dB/ 145ms	0.1mg/kg	10
Trachea SCM Carotid artery Parathyroid glands Skin neck	Total thyroidectomy	Quest Spectrum 2.0	30	22.5dB/ 50ms	1.5mg/ 1L blood volume	2.5

Abbreviations: ICG, indocyanine green, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle

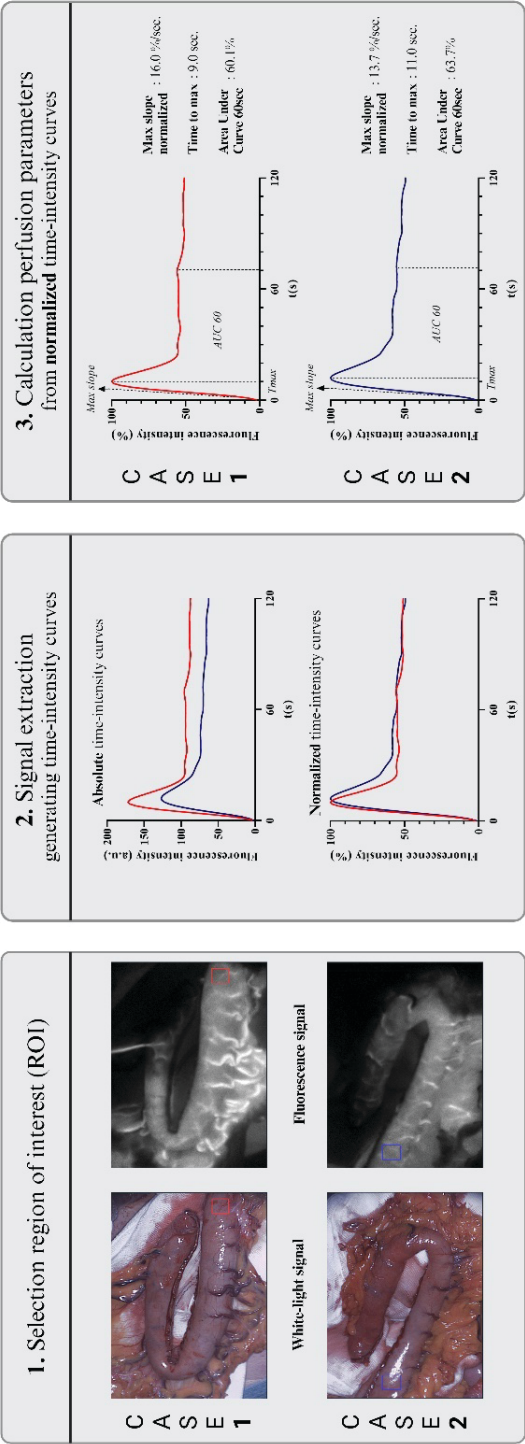


Figure. 1 Fluorescence signal quantification explained: establishment of time-intensity curves and perfusion parameters in two example cases. Abbreviations: t, time, a.u., arbitrary units



Results

Patient characteristics

A total of 178 patients (303 ROIs) were included in this study. Baseline patient characteristics are presented in Table 2. The mean age in the tissue groups ranged from 38.3 to 66.6 years and the mean body mass index ranged from 25.3 to 28.4. The proportion of females in the DIEP flap group was 100% and ranged from 13.2 to 93.3% in the other nine tissue groups. The colorectal resection cohort consisted of 30 patients, from which colon perfusion was analysed in 29 patients (30 ROIs) and ileum perfusion in 11 patients (11 ROIs). The gastric conduit cohort consisted of 53 patients. Nineteen patients undergoing a DIEP flap reconstruction were included, in which 29 perforators were identified. The skin foot cohort consisted of 16 patients with a total of 32 included feet. The total thyroidectomy cohort consists of 60 patients. From these patients, 52 ROIs of skin in the neck region, 44 ROIs of the trachea, 13 ROIs of the sternocleidomastoid muscle and 15 ROIs of the carotid artery were included. The parathyroid gland group consisted of 10 patients with 24 identified parathyroid glands.

Time-intensity curves and perfusion parameters

The mean normalized time-intensity curves with standard deviation for all tissues are illustrated in Fig. 2, and the mean absolute time-intensity curves are illustrated in Fig. 3. Parameter extraction of the target tissues is illustrated in Fig. 4 and Table 3. Three distinct perfusion patterns were identified across the analysed tissues, characterized by different inflow and outflow dynamics. Table 4 displays the parameters with overall and pairwise statistical comparison of perfusion metrics across three identified patterns.

Pattern one was observed in seven out of ten tissues and generally describes rapid inflow, followed by a brief outflow phase that transitioned into a stable state. The rapid inflow was marked by a short time to maximum intensity (T_{max} , medians between 13.0 – 17.8 s, total median 15.0 s) and a steep maximum normalised slope (medians between 12.6 – 0.6%/sec, total median 11.3%/sec). The outflow phase displayed median AUC60 values between 65.0 – 85.1%, with a total median of 74.5%. The tissues demonstrating this pattern included the colon, ileum, gastric conduit, trachea, carotid artery, parathyroid glands, and skin of the neck. Furthermore, the onset of fluorescence intensity in the carotid artery was always faster than any other adjacent tissue, demonstrating a median of 5.0 s (quartiles: 3.0 /5.5).

Table 2. Patient characteristics*

	Colon (n = 29)	Ileum (n = 11)	Gastric conduit (n = 53)	DIEP flap (n = 19)	Skin foot (n = 16)	Trachea (n = 44)	SCM (n = 13)	Carotid artery (n = 15)	Parathyroid gland (n = 10)	Skin neck (n = 52)
Age (years)	63.7 ± 12.2	62.9 ± 13.9	66.2 ± 6.9	53.7 ± 8.1	66.6 ± 12.3	49.4 ± 15.5	47.9 ± 13.1	47.1 ± 12.0	38.3 ± 11.4	48.9 ± 14.4
Female – n(%)	13 (44.8)	8 (72.7)	7 (13.2)	19 (100)	3 (18.8)	28 (63.6)	9 (69.2)	14 (93.3)	5 (50)	35 (67.3)
Body Mass Index	26.7 ± 5.4	25.3 ± 5.1	26.8 ± 4.2	28.4 ± 3.3	25.7 ± 3.6	27.0 ± 5.2	27.7 ± 5.3	26.1 ± 6.8	25.9 ± 6.1	27.2 ± 5.8
Diabetes – n(%)	4 (13.8)	1 (9.1)	8 (15.1)	1 (5.3)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension – n(%)	12 (41.4)	2 (18.2)	17 (32.1)	6 (31.6)	7 (43.8)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Kidney failure – n(%)	5 (17.2)	0 (0.0)	5 (9.4)	1 (5.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: m, male, f, female, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle

* Plus-minus values are means ± SD.

Table 3. Quantified ICG NIR fluorescence perfusion parameters for each tissue type

	Colon (n=30)	Ileum (n=11)	Gastric conduit (n=53)	DIEP flap (n=29)	Skin foot (n=32)	Trachea (n=44)	SCM (n=13)	Carotid artery (n=15)	Parathyroid gland (n=24)	Skin neck (n=52)
Tmax (s) Median (IQR)	13.3 (6.0)	13.0 (6.0)	15.0 (5.5)	24.0 (42.0)	141.4 (112.7)	16.3 (16.3)	22.0 (18.0)	16.0 (4.5)	14.5 (5.1)	17.8 (16.0)
Slope norm (%/s) Median (IQR)	12.0 (4.3)	12.6 (5.6)	10.6 (4.1)	9.3 (4.0)	2.1 (0.5)	10.9 (5.7)	9.7 (6.8)	12.5 (5.3)	11.5 (4.4)	10.8 (4.5)
AUC60 (%) Median (IQR)	65.6 (19.5)	65.0 (11.0)	68.8 (12.4)	89.1 (9.1)	N/A	85.1 (13.8)	89.0 (10.5)	78.1 (14.9)	76.5 (10.9)	77.4 (15.2)

Abbreviations: Tmax, time to max intensity, s, seconds, norm, normalized, AUC, area under the curve, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle, IQR, interquartile range, N/A, not applicable

Pattern two displays a reference curve with a slightly longer inflow period compared to pattern one, followed by a reduced outflow phase. This pattern was observed in the DIEP flap and sternocleidomastoid muscle (SCM) groups. The prolonged inflow phase was marked by longer median Tmax values of 22.0 (SCM) and 24.0 s (DIEP flap), and maximum normalised slopes of 9.3 (DIEP flap) and 9.7%/ second (SCM). The outflow phase demonstrated median AUC60 values of 89.0% (SCM) and 89.1% (DIEP flap). Pattern three demonstrates a distinct reference curve, characterised by a slow and long inflow phase, without reaching a peak and therefore not showing outflow within the first two minutes. This pattern was only observed in the skin of the foot group, and showed a median maximum normalised slope of 2.1%/second and inadequate Tmax and AUC60 values due to not reaching the outflow phase.

The Kruskal–Wallis test revealed significant differences in Tmax, slope norm, and AUC60 across the three perfusion patterns ($p < 0.001$). Pairwise comparisons using the Mann–Whitney U-test showed the following significant differences: Tmax and AUC60 were significantly different between pattern 1 and pattern 2 ($p < 0.001$), pattern 1 and pattern 3 ($p < 0.001$), and pattern 2 and pattern 3 ($p < 0.001$). Slope norm showed significant differences between pattern 1 and pattern 2 ($p = 0.044$), as well as between pattern 1 and pattern 3 ($p < 0.001$), and between pattern 2 and pattern 3 ($p < 0.001$).

Table 4. Statistical comparison of perfusion metrics across three identified perfusion patterns

Variable	Pattern 1	Pattern 2	Pattern 3	Overall comparison	Pairwise comparisons (p-value)
Tmax (s) Median (IQR)	15.0 (8.7)	24.0 (37.5)	141.4 (112.7)	$p < 0.001$	1 vs 2: <0.001 1 vs 3: <0.001 2 vs 3: <0.001
Slope norm (%/s) Median (IQR)	11.3 (4.8)	9.5 (4.5)	2.1 (1.4)	$p < 0.001$	1 vs 2: 0.044 1 vs 3: <0.001 2 vs 3: <0.001
AUC60 (%) Median (IQR)	74.5 (17.8)	89.0 (9.2)	97.4 (3.0)	$p < 0.001$	1 vs 2: <0.001 1 vs 3: <0.001 2 vs 3: <0.001

Abbreviations: Tmax, time to max intensity, s, seconds, norm, normalized, AUC, area under the curve, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle, IQR, interquartile range

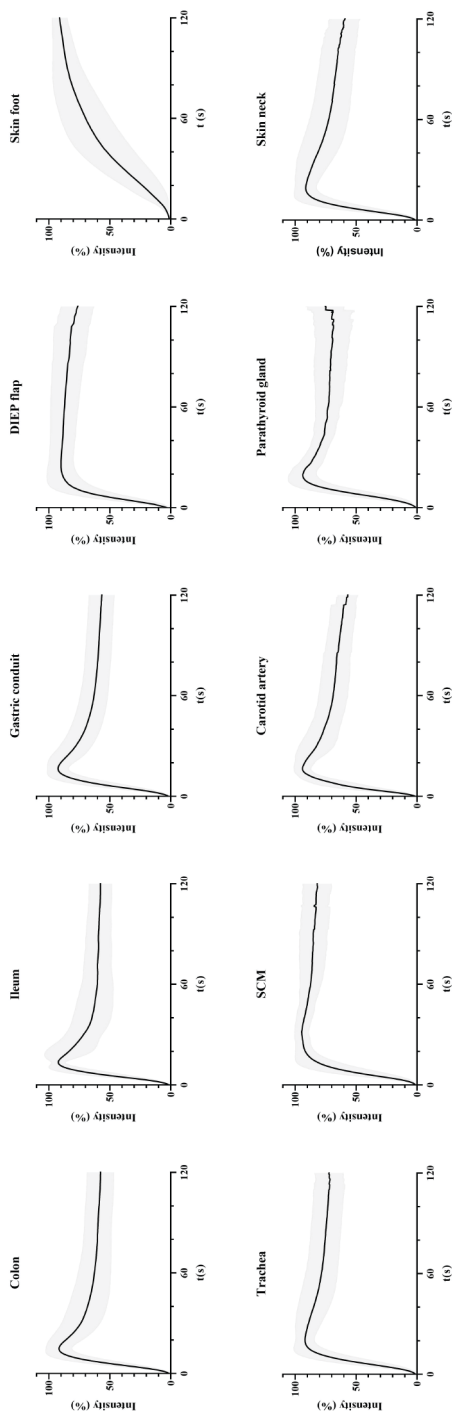


Figure. 2 Mean normalized time-intensity curves with standard deviation of the colon, ileum, gastric conduit, DIEP flap, skin foot, trachea, SCM, carotid artery, parathyroid gland and skin neck. Abbreviations: t , time, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle



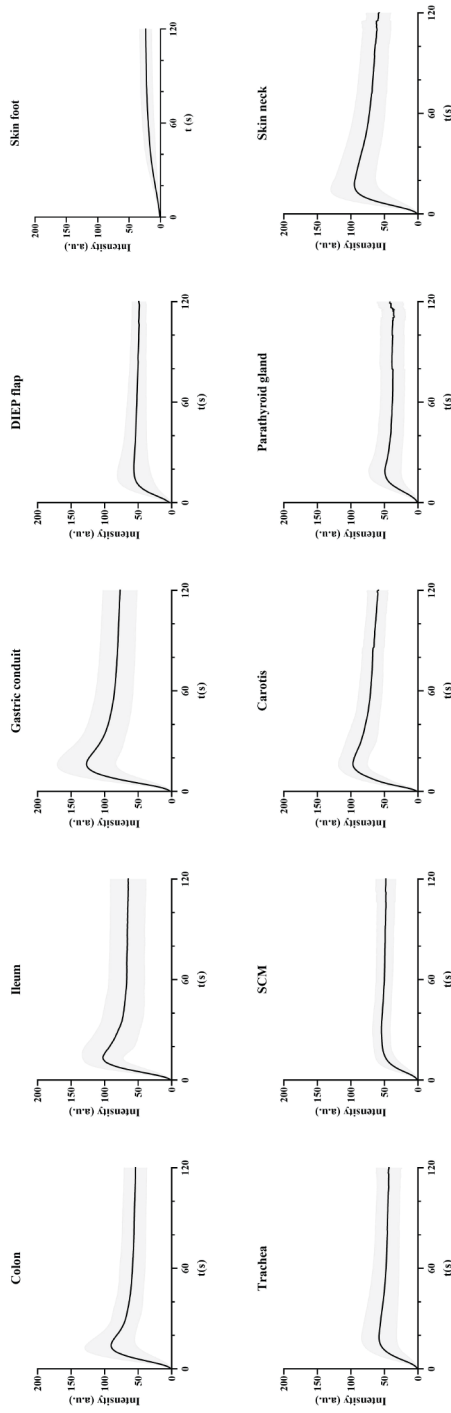


Figure. 3 Mean absolute time-intensity curves with standard deviation of the colon, ileum, gastric conduit, DIEP flap, skin foot, trachea, SCM, carotid artery, parathyroid gland and skin neck. Abbreviations: t , time, a.u., arbitrary units, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle

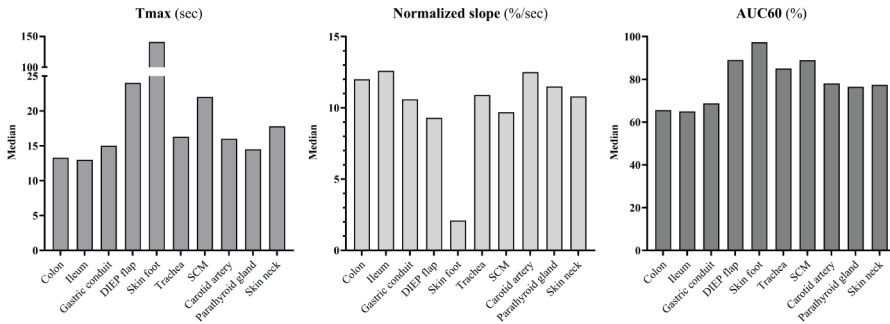


Figure. 4 The median values of the quantified perfusion parameters for each tissue type displayed in a bar chart. Abbreviations: sec, seconds, AUC, area under the curve, DIEP, deep inferior epigastric perforator, SCM, sternocleidomastoid muscle

Discussion

The establishment of reference curves to assess perfusion status using quantified ICG NIR fluorescence imaging is of paramount importance for the implementation of this technique in daily clinical practice. This study provides a first step towards this goal by displaying reference perfusion curves of ten unique, vital target tissues. First, seven out of ten target tissues demonstrated a similar pattern of reference curves. This curve was characterized by three stages, demonstrating a rapid inflow (1), a short period of outflow (2) followed by a gradual or absent outflow (steady state) (3). Outliers of these reference curves were the foot of the skin (gradual, slow inflow), the DIEP flap and the sternocleidomastoid muscle (reduced outflow). Secondly, normalized analysis of the data proved to be the most consistent method for establishing these reference curves, with the normalized slope demonstrating the least variance. Displaying these reference curves for vital tissue perfusion is important since most studies on quantitative ICG NIR fluorescence have predominantly focused on perfusion assessment of tissue at risk.^{5, 36–38}

In earlier studies on quantified ICG NIR fluorescence imaging, considerable clinical value in multiple perioperative settings was shown, such as intraoperative identification of malperfusion to prevent dreaded ischemia-related complications.^{19, 23, 37, 39} Furthermore, pre- and postoperative applications also arise, including the objective evaluation of wound perfusion or quality control for a perfusion-enhancing intervention such as a peripheral bypass.^{25, 40, 41} These studies investigated absolute, relative, and time-related parameters, but showed comparable curves of malperfusion, generally described as prolonged inflow and reduced outflow. In the present study, variations in reference curves were observed within tissues, for which several explanations can be given. The only tissue showing an apparent variation of inflow was the skin of the foot, characterised by a slow inflow with low normalized slope, and high Tmax values. This variation could be explained by the distal location of this tissue from the central blood supply.

Furthermore, the DIEP flap and SCM showed a noticeable minimal amount of outflow, with a slight delay of inflow. In the DIEP flaps, this finding could be explained by the absence of collateral flow resulting in less outflow of ICG in the flap. For the SCM, the limited outflow could be explained by the retraction of the muscle during surgery and imaging, impeding outflow. The other seven tissues demonstrated comparable reference curves of vital tissue perfusion with rapid inflow, a period of outflow followed by a gradual or absent outflow (steady state), a pattern which has also been described in literature as adequate perfusion.^{29, 30, 42} The absolute time-intensity curves displayed in this study showed the anticipated large variation between curves, emphasizing the inaccuracy of intensity-related (absolute) parameters once again.^{35, 43, 44} A limitation of this study is the inclusion of data from five separate cohorts with varying imaging protocols (e.g. camera distance, ICG dosage). While normalization reduced variability and allowed for consistent reference curves within this study, it remains uncertain to what extent such variations, or the use of different commercially available devices, may impact fluorescence parameters.

Furthermore, the influence of patient-specific factors like hemodynamics (e.g. blood pressure, cardiac output) on a time-intensity curve is known, however, the limited evidence makes correction for these factors not yet achievable.^{33, 45–48} Another limitation of this study is that the vitality of the analysed tissues in this study was presumed, however, not completely guaranteed as it was clinically assessed and most tissues were measured in an operative setting. Additionally, the selection of ROIs involved variation in size and location across different tissue types, tailored to the specific anatomical and physiological characteristics of each tissue. While this approach ensured relevance and consistency, it may also introduce a degree of variability in the results. Since an objective method for intraoperative tissue perfusion assessment is still lacking, the use of clinical assessment as the predominant mode of evaluation seems justifiable. Added to this, the observed minimal variation among the normalized curves within the tissue groups underscores the likelihood of selectively identifying vital tissue.

The significant differences observed in Tmax, Slope norm, and AUC60 across the three perfusion patterns suggest that these patterns reflect distinct physiological states, which could be of clinical relevance in assessing tissue perfusion. The tested tissue groups varied in sample size and the calculated p-values were not corrected for multiple comparisons due to the descriptive nature of this study and small sample sizes, therefore the results should be interpreted accordingly. The clinical utility of these patterns will require further validation, particularly in defining clinically relevant thresholds for differentiating between good and poor perfusion.

Therefore, dedicated clinical studies evaluating perfusion curves of tissue in vital and malperfused states, including clinical outcomes, will be needed to address the predictive value of quantified perfusion parameters for assessing the risk of postoperative perfusion related complications. Moreover, better comprehension of tissue perfusion curves in various conditions is needed to determine the technique's ability to distinguish arterial and venous pathology.

The use of artificial intelligence (AI) is a promising approach to address challenges associated with perfusion assessment using quantitative ICG NIR fluorescence. Despite the clinical promise, the challenges of interpreting results objectively, standardizing imaging protocols, and accounting for patient-specific factors necessitate innovative solutions. AI models have the potential to provide invaluable insights into the detection of perfusion deficits and underlying pathologies [49]. Such AI-driven analysis, possibly combined with other innovative techniques like hyper-spectral imaging, could address the full clinical potential of quantitative perfusion assessment, enhancing its precision and reliability in diverse perioperative settings.⁵⁰ Building on the insights provided in this study, this technique holds significant potential to become a key tool in preventing complications related to malperfusion in diverse surgical settings, such as anastomotic leakage or skin necrosis. Its clinical adoption could markedly enhance perioperative decision-making and improve patient outcomes.

Conclusion

This study is the first to describe reference curves for vital tissue perfusion in ten target tissues using quantified NIR fluorescence imaging with indocyanine green, providing a benchmark for adequate perfusion. These findings mark an important step towards the clinical implementation of this technique and highlight its potential to provide surgeons with an objective and reliable tool for perioperative perfusion assessment.

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