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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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Chapter 1



Introduction and thesis outline



Introduction

Across surgical specialties, dreaded complications such as non-healing wounds, anastomotic leakage, and flap necrosis remain a major cause of morbidity. For instance, anastomotic leakage can occur in up to 41% of colorectal and oesophageal resections, fat necrosis in free flap surgery is reported in up to 35%, and non-healing ulcers contribute to high rates of amputation in patients with peripheral arterial disease (PAD) ⁽¹⁻⁹⁾. These events are associated with prolonged hospital stay, increased health care costs, and substantial impact on patients' quality of life ⁽¹⁰⁻¹⁵⁾. A common underlying factor in these complications is inadequate tissue perfusion ⁽¹⁶⁻¹⁹⁾. While essential diagnostic tools exist to evaluate macrovascular patency, such as ankle-brachial index, duplex ultrasound, and angiographic techniques, they fail to capture local tissue perfusion. It is precisely at this microvascular level that surgical outcomes are most directly determined, yet no objective method is currently available to assess local microvascular perfusion perioperatively. This diagnostic gap continues to challenge surgical decision-making, limiting the ability to predict tissue healing, tailor interventions, and prevent complications.

Near-infrared fluorescence (NIRF) imaging with indocyanine green (ICG) has been increasingly evaluated in clinical studies as a technique to visualize tissue perfusion. The technique combines the intravenous injection of the fluorescent dye ICG with illumination by near-infrared light and capture by a dedicated camera system, producing a dynamic image of tissue perfusion. This imaging modality is attractive because it relies on a safe intravenous dye that remains intravascular, thereby providing a real-time representation of local blood flow with up to 1cm of penetration depth. Over the past decade, NIRF imaging has found applications across various surgical domains, including vascular, gastrointestinal and reconstructive surgery. In these settings, visual interpretation of the fluorescence signal has been the primary approach. While larger clinical studies, including randomized trials, have shown that this can yield significant findings, interpretation remains qualitative and subject to considerable interobserver variability, which is increasingly recognized as a major limiting factor ^(20, 21).

Quantitative analysis of the fluorescence signal has been explored as a way to overcome the limitations of visual assessment. Instead of relying on a single visual impression, the recorded video of the fluorescence signal can be converted into a time-intensity curve, derived from a selected region of interest (ROI) in the tissue that reflects the inflow and outflow of ICG and thereby tissue blood flow. From these curves, perfusion parameters such as time-to-maximum intensity, inflow slope, or outflow characteristics can be calculated. These metrics provide a numerical representation of perfusion, enabling objective and reproducible evaluation ⁽²²⁻²⁴⁾. In this way, quantification offers the potential to detect perfusion differences that may remain hidden to the human eye.

As a result, it has evolved into an active field of research, in which different perfusion parameters are being explored for their robustness and clinical relevance.

Despite this promise, several challenges currently limit the clinical implementation of quantitative ICG analysis. Research groups have applied different acquisition protocols, varying in aspects such as camera distance, ICG dosage, and imaging systems, but it remains unclear which of these factors contribute to variability in specific perfusion parameters and to what extent they influence the results ^(22, 25-27). In addition, no consensus exists on which perfusion parameters are most clinically relevant or how thresholds should be defined ^(23, 28). Furthermore, most investigations have been confined to single subspecialties, further restricting the generalizability of findings. Together these issues highlight the need not only for methodological standardization, but also for systematic evaluation of applicability and clinical relevance across surgical domains.

This thesis addresses these gaps by evaluating quantitative ICG fluorescence imaging across multiple surgical specialties and clinical contexts. The studies cover vascular surgery, colorectal and oesophageal surgery, and reconstructive flap surgery, settings in which tissue perfusion is a critical determinant of clinical outcome. Beyond demonstrating feasibility and clinical applicability, the work critically examines variations in imaging protocols, how this affects quantitative outcomes and explores strategies such as normalization to improve comparability of data. Furthermore, the introduction of reference curves for multiple vital tissues represents an important step toward standardized interpretation, enabling results to be more widely generalizable.

The central aim of this thesis is to determine how quantitative ICG fluorescence analysis can contribute to a more objective assessment of tissue perfusion. By addressing both domain-specific applications and cross-disciplinary standardization, this thesis moves beyond isolated investigations and provides a broader foundation for advancing the technique from experimental use toward clinical implementation. Reliable perfusion assessment using quantitative NIRF imaging could provide surgeons with a valuable tool to refine surgical strategies, support data-driven decision-making, and reduce complications related to inadequate tissue perfusion.

Thesis outline

This thesis consists of eight chapters. **Chapter 1** provides a general introduction to this thesis, describing the clinical relevance of tissue perfusion within surgery, current diagnostic limitations, and the potential of near-infrared fluorescence (NIRF) imaging with indocyanine green (ICG), focusing on the added value of quantitative signal analysis. **Chapters 2 and 3** are set within the field of vascular surgery and focus on patients with peripheral arterial disease (PAD). These chapters address the broader question of how revascularization procedures can be optimized. **Chapter 2** evaluates the potential of quantitative NIRF imaging to predict clinical outcomes after revascularization. **Chapter 3** examines the applicability of the angiosome concept in PAD patients by comparing perfusion outcomes in directly and indirectly revascularized angiosomes.

Chapters 4 and 5 focus on gastrointestinal surgery, with the common aim of assessing feasibility and characterizing quantitative perfusion patterns in tissue at risk of anastomotic leakage. **Chapter 4** investigates intraoperative perfusion measurements in colonic tissue before resection. **Chapter 5** describes intraoperative perfusion measurements in gastric conduits prior to cervical anastomosis.

Chapter 6 presents the protocol of a multicenter randomized controlled trial, designed to evaluate whether NIRF imaging can reduce fat necrosis after deep inferior epigastric perforator (DIEP) and muscle-sparing transverse rectus abdominis myocutaneous (ms-TRAM) flap breast reconstructions.

Chapter 7 takes a broader scope, investigating the establishment of quantified reference curves for vital tissue perfusion across multiple tissues, based on measurements obtained in five study cohorts from three hospitals.

Finally, **Chapter 8** provides a general discussion of the findings presented in this thesis, their implications for future research, and the potential role of quantitative NIRF imaging in surgical decision-making.

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