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NEW TECHNOLOGY

Continuous organ perfusion monitoring using indocyanine green in a piglet model

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Abstract

Background Unrecognized organ hypoperfusion may cause major postoperative complications with detrimental effects for the patient. The use of Indocyanine Green (ICG) to detect organ hypoperfusion is emerging but the optimal methodology is still uncertain. The purpose of this study was to determine the feasibility of real-time continuous quantitative perfusion assessment with Indocyanine Green (ICG) to monitor organ perfusion during minimally invasive surgery using a novel ICG dosing regimen and quantification software.

Method In this experimental porcine study, twelve subjects were administered a priming dose of ICG, followed by a regimen of high-frequency (1 dose per minute), low-dose bolus injections with weight-adjusted (0.008 mg/kg) ICG allowing for continuous perfusion monitoring. In each pig, one randomly assigned organ of interest [stomach ($n=3$), ascending colon ($n=3$), rectum (n = 3) and spleen ($n=3$)] was investigated with varying camera conditions. Video recording was performed with the 1588 AIM Stryker camera platform and subsequent quantitative analysis of the ICG signal were performed using a research version of a commercially available surgical real-time analysis software.

Results Using a high-frequency, low-dose bolus ICG regimen, fluorescence visualization and quantification in abdominal organs were successful in the stomach (3/3), ascending colon (1/3), rectum (2/3), and the spleen (3/3). ICG accumulation in the tissue over time did not affect the quantification process. Considerable variation in fluorescence signal was observed between organs and between the same organ in different subjects. Of the different camera conditions investigated, the highest signal was achieved when the camera was placed 7.5 cm from the target organ.

Conclusion This proof-of-concept study finds that real-time continuous perfusion monitoring in different abdominal organs using ICG is feasible. However, the study also finds a large variation in fluorescence intensity between organs and between the same organ in different subjects while using a fixed weight-adjusted dosing regimen using the same camera setting and placement.

Keywords Indocyanine Green · Continuous perfusion monitoring · Abdominal surgery · Quantitative perfusion assessment · Fluorescence

Unrecognized organ hypoperfusion may cause severe postoperative complications following abdominal surgery with detrimental outcome for the patients [1]. Accurate identification of the vascular anatomy with significant individual variation is a challenge even for skilled and experienced surgeons and of general concern in such cases [2, 3].

Indocyanine green (ICG) is a fluorophore that, when injected intravenously and exposed to near-infrared light (NIR), allows for evaluation of the tissue perfusion using its fluorescent properties [4].

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This allows the surgeon to perform ICG fluorescence imaging as an aid in intraoperative decision-making [5–7].

ICG fluorescence imaging is performed either qualitatively or quantitatively. Currently, the qualitative assessment is the most common method of use. It is based on the surgeon's subjective evaluation of the ICG signal while the quantitative assessment is performed objectively using an image analysis software. While qualitative analysis of ICG has the advantage of being available instantly during an operative procedure, it also has limitations such as subjective interpretation of the fluorescent signal. Additionally, conditional factors such as distance to the camera, ICG dosage, intersubject variation and contamination with white light can highly influence the qualitative assessment. Quantitative ICG assessment is an emerging method currently in development and may be less susceptible to these limitations. Quantitative ICG perfusion assessment is performed by a computational evaluation of the time-dependent ICG signal and can be performed in real-time [8–12].

Due to accumulation of ICG in the tissue and a maximum recommended dosage of ICG (5 mg/kg) [13], the contemporary application of ICG perfusion assessment only allows for a limited number of qualitative evaluations during each surgery [14]. However, the emergence of the quantitative ICG perfusion assessment potentially allows for similar tissue evaluation at much lower ICG dosage which enables a continuous, instead of a momentary, observation of tissue perfusion.

We hypothesize that quantitative perfusion assessment with a high-frequency, low-dose bolus ICG regimen can be used for continuous organ perfusion monitoring during abdominal surgery. The purpose was to investigate the feasibility of this methodology in four different abdominal organs and under different camera conditions as a proof-of-concept study.

Materials and methods

Animals

The study was conducted at the Department of Experimental Medicine (AEM), University of Copenhagen. Twelve female domestic piglets weighing between 16 and 32 kg were used in this non-survival study. Only pigs assessed as clinically healthy without clinical disease and with normal body temperature were chosen. Animals were excluded from the study if the animal died or needed to be euthanized prematurely during surgery due to hemodynamic instability. Single randomization was used to pair each animal with a target organ during surgery.

The study was conducted in accordance with the guidance and approval of the national animal ethics committee (Approval Nr. 2021-15-0201-00,924) and is reported according to the recommendations of the ARRIVE guidelines [15].

Anesthesia, fluid administration, ventilation and euthanasia

Before surgery, the animals were sedated with 20–25 mg/kg ketamine and 0.5–0.7 mg/kg midazolam, both intramuscular. Ear veins were cannulated bilaterally, and if necessary, anesthesia was deepened with 1–4 mg/kg propofol before orotracheal intubation. Anesthesia was maintained with sevoflurane 2–2.5%. All pigs were mechanically ventilated, and settings were aimed at normoventilation with FiO2 at 60%.

Analgesia was achieved with a bolus of 5–20 µg/kg fentanyl i.v. and followed with a continuous rate infusion of 10–100 µg/kg/h fentanyl i.v. depending on nociceptive responses.

The femoral artery and vein were cannulated for fluids and ICG administration. Vital parameters, i.e., ETCO2, SpO2, ECG, and direct arterial blood pressure, were continuously monitored. At the end of the surgery, the anesthetized animals were euthanized by a rapid i.v. injection of pentobarbital 140 mg/kg. ECG and blood pressure recordings confirmed asystole and circulatory arrest.

Pilot case

To determine the most suitable regime for real-time continuous perfusion monitoring, we tested different ICG dosages and time intervals in one subject, termed the "pilot case".

Boluses ranging from 0.1 to 0.3 mL with weight-adjusted dosages between 0.004 mg/kg and 0.01 mg/kg were administered in predetermined time intervals, recorded, and subsequently assessed. In addition, the low-dose bolus injection necessitated the use of a "priming dose" in the beginning of each recording to assure the recording of a sufficient ICG signal in the beginning of the measurements.

Surgical preparations and measurements

Twelve piglets were randomly allocated to one of the four target organs: Stomach (piglet 1, 2 and 12), ascending colon (piglet 3, 8 and 11), rectum (piglet 4, 9 and 10) and spleen (piglet 5, 6 and 7).

After pneumoperitoneum (12 mmHg), three laparoscopic ports (5–12 mm) were placed. A 10 mm, 30-degree laparoscope (Stryker, 1588 AIM HD Camera System) was inserted through a suprapubic port, and the organ of interest was visualized. The camera was fixed at a 7.5 cm distance of the organ in a mechanical holding arm.

The pump driven ICG administration was initiated with a priming dose and followed by a high-frequency (60 s interval), low-dose bolus administration of ICG (Micrel

Rythmic™ Evolution). The measurement was performed with four different camera conditions:

Condition 1 The camera optic was placed perpendicular to the anatomical structure of interest at a 7.5 cm distance for 8 min.

Condition 2 The camera optic was placed perpendicular to the anatomical structure of interest at a 15 cm distance for 8 min.

Condition 3 The camera optic was moved approximately 10 cm to the left, so that the organ part, that was previously centered, was now visible in the periphery of the screen. The camera distance remained at 15 cm. Recording in this position proceeded for 4 min.

Condition 4 The camera optic was slowly moved around the borders of the organ for 4 min, switching distances between approximately 7.5 and 15 cm.

Method of quantitative perfusion assessment

The resulting fluorescence intensity signal was recorded and postoperatively analyzed using a research version of a commercially available surgical real-time analysis software for quantitative perfusion assessment (PerfusionWorks, Perfusion Tech Aps, Denmark) adapted for continuous perfusion monitoring. The software is developed for real-time, intraoperative quantitative ICG assessment and is controlled from an external tablet or laptop with video-input from the surgical platform. It can also be used to analyze preexisting video material.

The software allows the surgeon to choose size-adjustable regions of interest (ROI). From each ROI the software provides information on the perfusion status of that specific anatomical area. The software has a motion correction algorithm that allows the ROI to follow the selected tissue thus mitigating the impact of movement of the abdominal organs. In this experimental study we selected a central ROI and a peripheral ROI on the recording screen for perfusion quantification analysis during each camera condition (C1, C2, C3 and C4). In this experimental study, both ROIs were chosen retrospectively, aiming for the same anatomical field in all four conditions.

The software creates an ICG fluorescence time-intensity curve from each ROI, and the perfusion metrics are extracted with each inflow of ICG. The following perfusion metrics were analyzed in this study: F_{max}—maximal fluorescent signal intensity, T_0—time from ICG injection until first recording of fluorescent signal, T_{max}—time from first fluorescent signal to maximal intensity, $T_{1/2max}$- time until 50% of maximal fluorescence intensity is reached, *Slope* (F_{max}/T_{max},) and TR–time ratio ($T_{1/2\ max}/T_{max}$,) (Fig. 1). Means and standard deviations (SD) of the perfusion metrics were calculated from each condition.

Results

All subjects completed the experiment. During the procedure, all animals remained hemodynamically stable.

Analysis of the quantitative ICG signal was feasible when injecting 0.008 mg/kg every 60 s. The low-dose bolus injection necessitated the use of a "priming dose" at the beginning of each measurement to assure a sufficient ICG fluorescence signal. In the pilot case, we found 0.056 mg/kg of ICG solution to be the optimal priming dose.

With this dose, we were able to detect a fluorescent signal in the stomach (3/3 subjects) ascending colon (2/3 subjects), rectum (2/3 subjects), and in the spleen (3/3 subjects) (Table 1).

In condition 1 with the high-frequency low-dose ICG administration regimen we were able to detect a fluorescent signal sufficient for quantification in the central ROI (yellow curve) in the stomach (3/3 subjects) (Fig. 2), ascending colon (1/3 subjects) (Fig. 3), rectum (2/3 subjects) (Fig. 4), and in the spleen (1/3 subjects) (Fig. 5) (Table 1). The peripheral ROIs (red curve) showed synchronous changes in the time-intensity curve compared to the central ROIs, although showing a dissimilar configuration and at a lower intensity.

A gradual increase in the baseline ICG intensity due to accumulation from each administration was measured in almost all subjects (Figs. 6, 7, 8, 9). Qualitative visual saturation, characterized by the organ emitting bright green fluorescence, was observed over time in the stomach, ascending

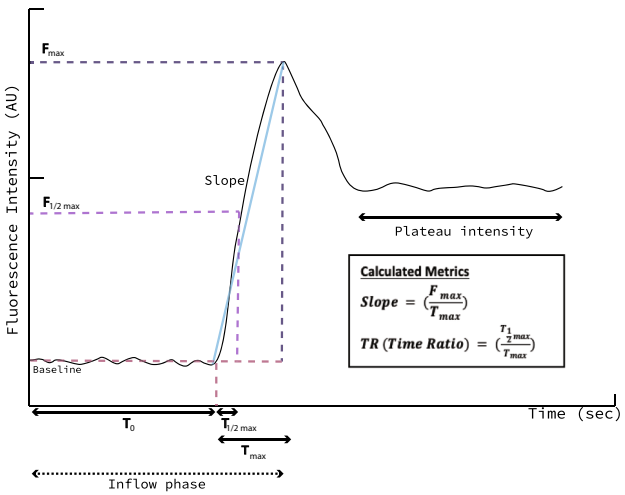


Fig. 1 A graphic depicting different quantitative ICG metrics, including F_{max}—maximal fluorescent signal intensity, T_0—time from ICG injection till first recording of fluorescent signal, T_{max}—time from first fluorescent signal to maximal intensity and $T_{\frac{1}{2}max}$—time until 50% of maximal fluorescence intensity is reached (Color figure online)

Table 1 Results of qICG recordings in ROI 1 (central). ✓ qICG analysis was possible and ICG signal detectable by the quantification software. ✗ qICG analysis was not possible due to no or insufficient ICG signal

Animals	Ventricle			Ascending colon			Rectum			Spleen		
	1	2	12	3	8	11	4	9	10	5	6	7
Priming dose	✓	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓	✓
Condition 1	✓	✓	✓	✓	✗	✗	✓	✓	✗	✓	✗	✗
Condition 2	✓	✓	✓	✓	✗	✗	✓	✓	✗	✓	✗	✗
Condition 3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

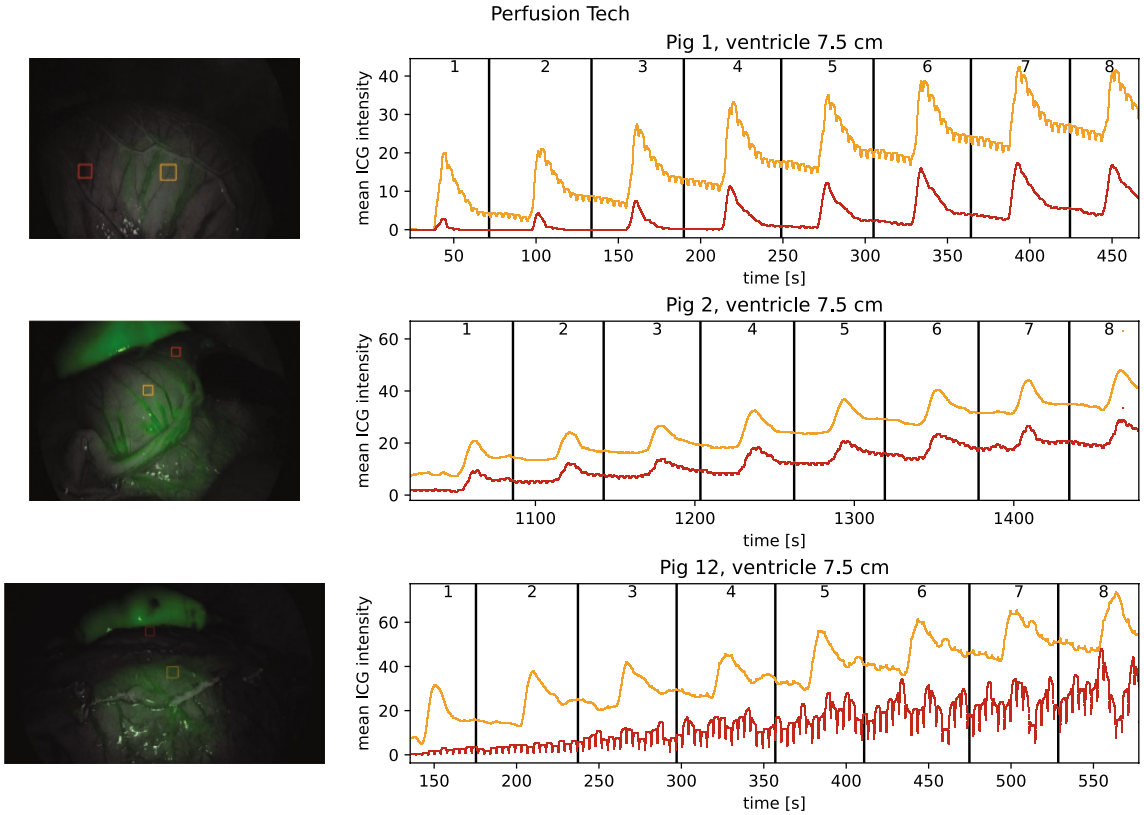


Fig. 2 Baseline perfusion measurement of the ventricle after priming dose. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

colon and rectum but did not interfere with the quantitative software recording and analysis.

Figures 6, 7, 8, 9 show representative examples of the organ-specific time-intensity curves, recorded in C1, C2, and C3. Mean and SD of *Slope*, F_{max}, T_{max}, $T_{1/2\,max}$ and TR were calculated based on each time-intensity curve.

T_{max} and TR appear very stable in the stomach and ascending colon in measurements during conditions 1 and 2, with homogenous oscillation curves in both ROI 1 (yellow) and ROI 2 (red).

In contrast, there can be seen big variance in F_{max} in the rectum with the centrally placed ROI 1 registering much steeper and higher oscillation curves than the more peripherally placed ROI 2.

Condition 4, in which we moved the camera during the recording, switching between different distances from the organ, did not produce a reproducible signal, due to too much disturbance, caused by the irregular movement.

Discussion

This proof-of-concept study, with its novel high-frequency low-dose ICG bolus administration regimen, aims to be the first step towards developing a tool that can aid the surgeons' decision-making during abdominal surgery.

Our results show that the methodology of continuous ICG perfusion assessment during surgery is technically possible. We believe to have identified three key findings that may

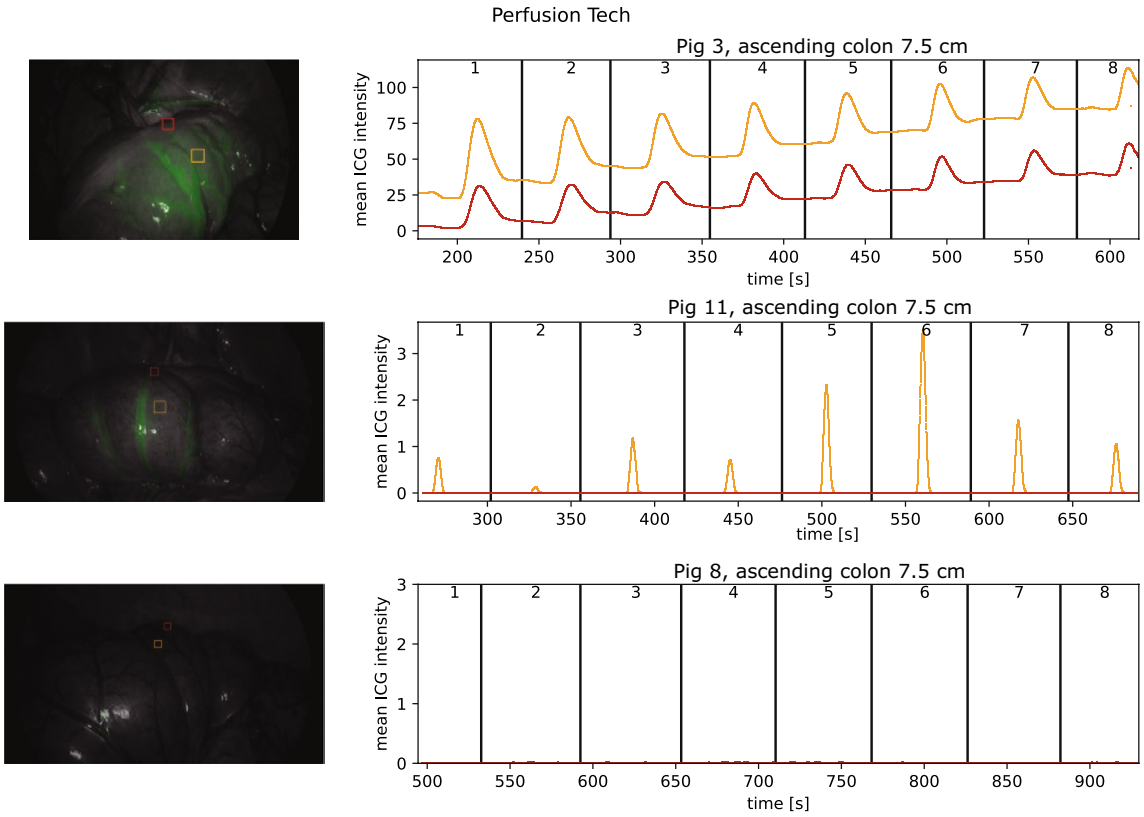


Fig. 3 Baseline perfusion measurement of the caecum after priming dose. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

be important in facilitating successful continuous perfusion monitoring and provide a platform for further developments in the future.

First and most importantly, the dose of ICG to be administered should be low enough to allow continuous bolus administration over several hours without exceeding the recommended maximum daily dosage of 2 mg/kg, while simultaneously providing a sufficient signal-to-noise ratio for reliable perfusion monitoring. For this study, we used a pilot case and determined the most suitable dose to be 0.008 mg/kg. To put this into perspective, the weight-adjusted ICG bolus doses currently used in colorectal surgery vary between 0.2 and 0.3 mg/kg [9, 16]. We decided on a "one size fits all" approach and standardized the priming dose given at the beginning of each recording, expecting that the same weight-adjusted ICG dose would suffice to cause an adequate signal-to-noise ratio in all study subjects.

Using this new dosing regimen, recording and analyzing continuous fluorescence time-intensity curves in various organs, was possible. When the ICG fluorescent signal was sufficient, each low-dose ICG bolus resulted in a distinguishable time-intensity curve, representing a well-perfused organ area. However, our standardized dosing regimen resulted in recognizable heterogeneity when comparing measurements in different organs, as well as the same organ in different subjects. It has been shown that ICG fluorescence intensity does not only depend on the injected dose, but might be influenced by outside factors, such as temperature, pH status and light conditions [17]. Furthermore, differences in tissue thickness and anatomical variances could possibly aggravate quantitative measurements using such low doses of ICG. This may explain the high individual variability, but the exact reason as to why the priming dose did result in varying signal intensity is uncertain. In all three subjects, spleen recordings had a low signal-to-noise ratio, which caused less stable oscillation recordings. This is most likely explained by the anatomical structure of the spleen, consisting primarily of red pulp. A study on splenic ICG perfusion analysis after spleen-preserving distal pancreatectomy did record organ fluorescence in all subjects [18]. However, the researchers used a much higher ICG dose (0.15 mg/kg), indicating that our standardized dose (0.008 mg/kg) was likely too low to cause a strong signal in the spleen, which was the only solid, of otherwise hollow organs investigated in this study.

We furthermore suspect, that the measurement of ROI 2 in Pig 7 is giving a false positive oscillation signal. Due to the anatomical curving of the organ, the fluorescent border

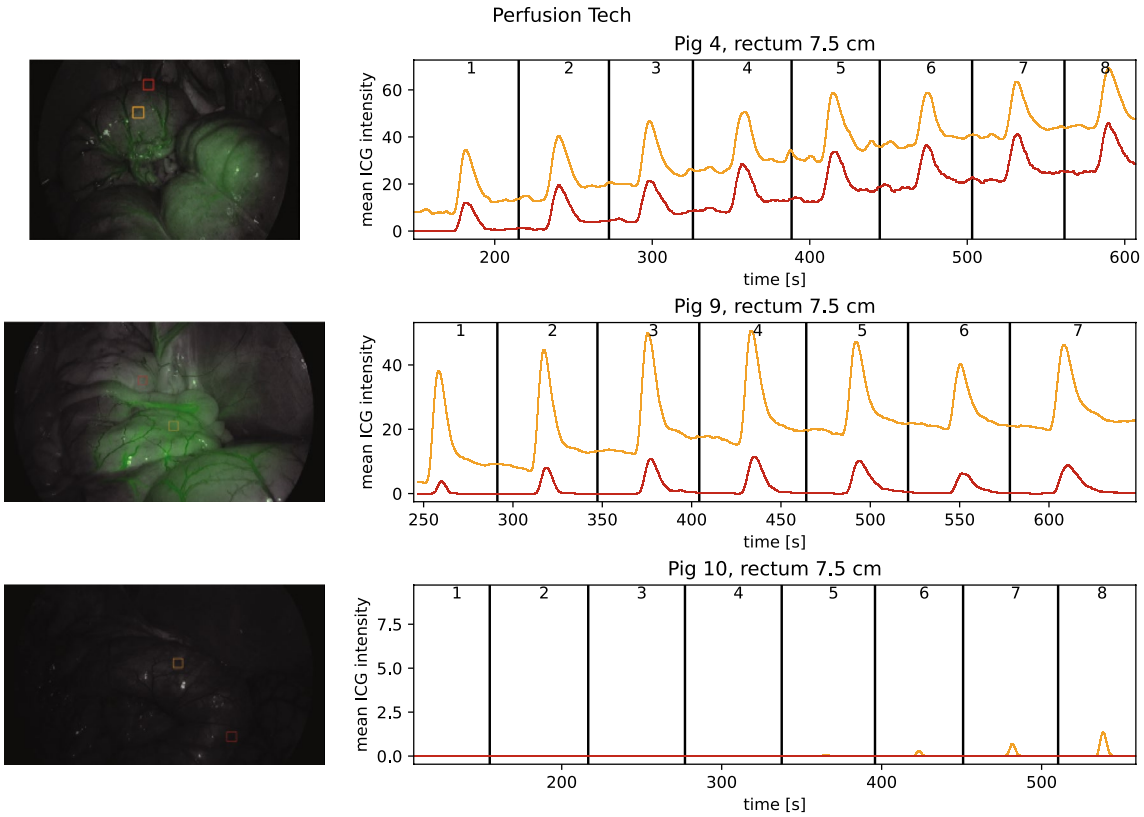


Fig. 4 Baseline perfusion measurement in the rectum after priming dose. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

is most likely caused by the reflection of the diaphragma tissue located below the spleen. This might explain, why the resulting oscillation recordings appear atypical and why the fluorescence intensity of ROI 2 is higher than that in ROI 1.

Therefore, we suggest that future studies should ideally be conducted with an adjustable priming dose that allows initiation of the high-frequency low-dose ICG administration regimen only after a sufficient signal-to-noise ratio has been achieved.

Secondly, standardization of recording conditions is essential for analyzis and evaluation of continuous perfusion monitoring. We followed a standardized design, shifting between three different conditions (C1: 7,5 cm distance from organ, C2:15 cm distance from organ, and C3: peripheral from organ), and chose a centrally and peripherally placed ROI for our analyzis. Of the three conditions, condition 1 appeared to be the most favorable for perfusion assessment. Increasing the camera-organ distance led to a decrease or disappearance of the ICG signal. Notably, a decreased signal-to-noise ratio still allowed for perfusion assessment in most organs. Recordings of condition 4, in which the camera was moved around by the surgeon, were not usable for perfusion assessment because of heavy "noise" created by the movement. While these observations should be interpreted with caution due to our small sample size, T_{max} and TR appear favorably stable, when comparing the metrics in different organs as well as in condition 1 and 2.

In contrast, condition 1 in the rectum is a good example of F_{max} being heavily dependent on the camera angle and distance from the camera to ROI, with the centrally placed ROI 1 registering much steeper and higher oscillation curves than the more peripherally placed ROI 2.

Thirdly, we observed that ICG accumulation and visual saturation over time did not interfere with the quantitative analysis. In this study, an organ was considered visually "saturated," when its radiance of bright green fluorescence had reached a subjective maximum intensity. While an organ saturated with ICG does not allow for further qualitative analyzis of the ICG signal, we did not reach a "saturation limit" that prohibited us from performing quantitative analyzis of the individual bolus signals during the experiment and can therefore be used even during longer procedures.

The strength of this study lies in its standardized design, which allows for comparison of results between single subjects. We used a pilot case to determine the most appropriate dosing regime, which we followed in all study subjects. This resulted in important insights into the dynamics of low-dose ICG boluses that are essential for developing this novel methodology further.

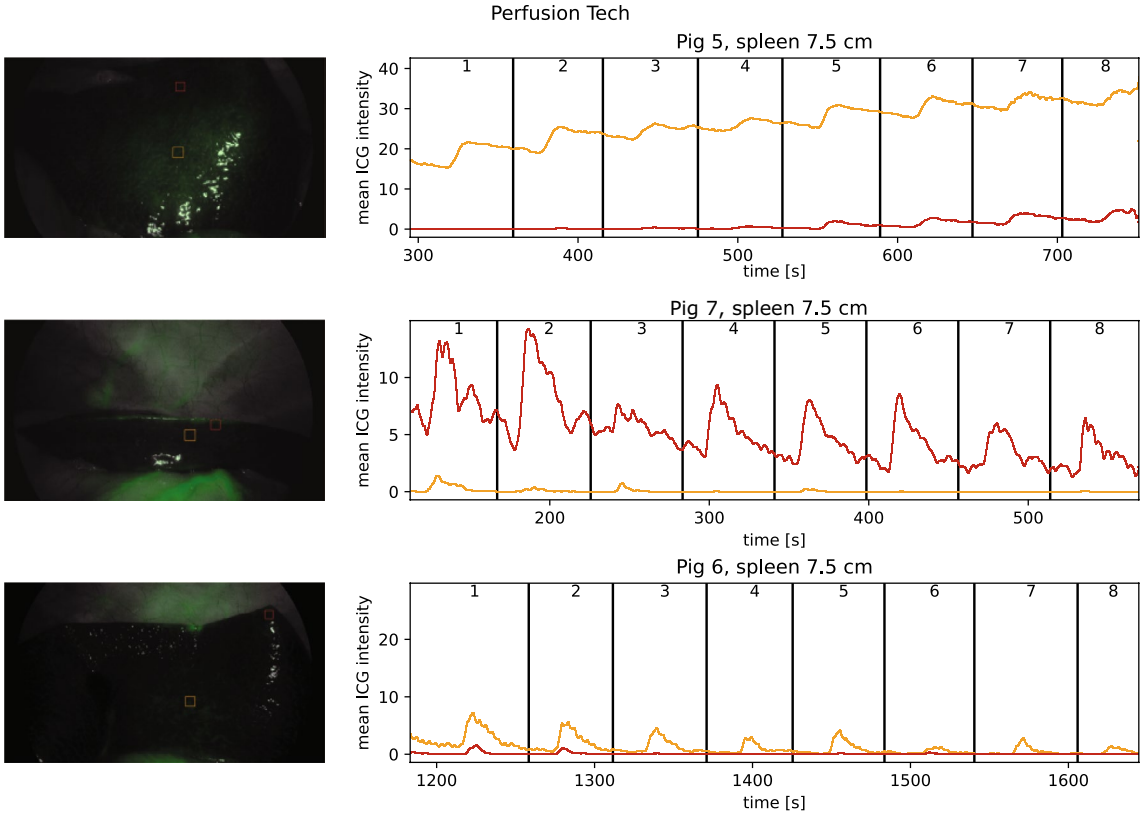
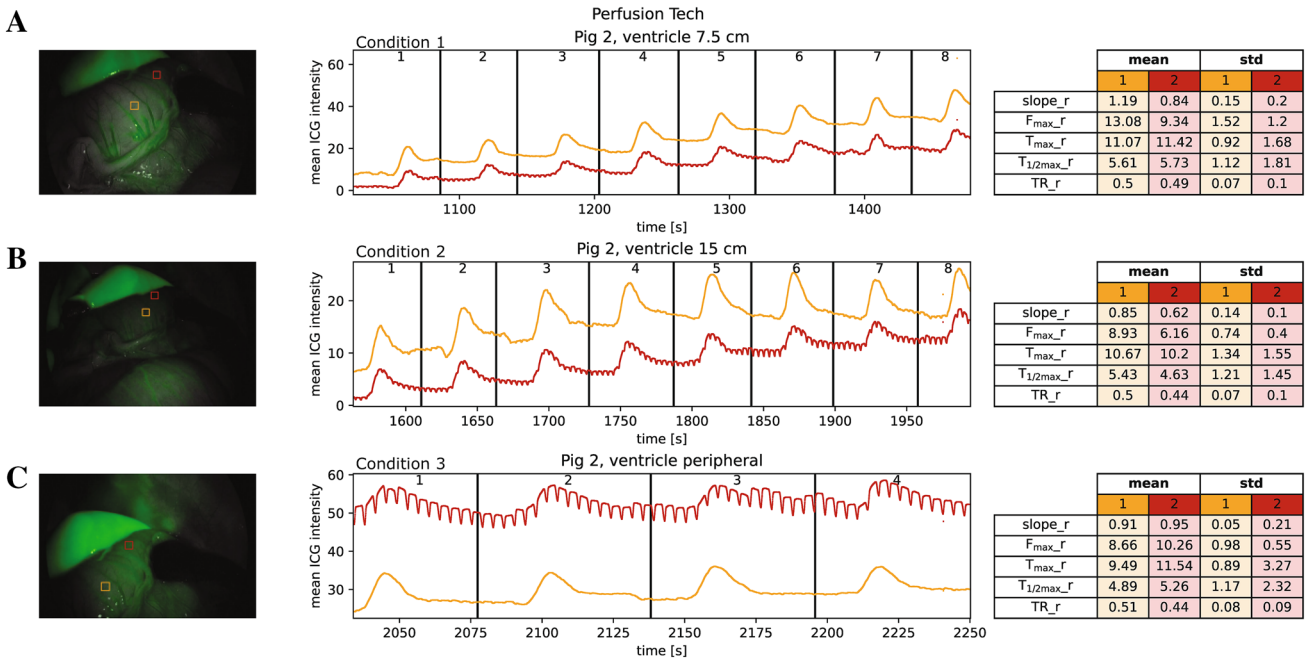


Fig. 5 Baseline perfusion measurement of the spleen after priming dose. Yellow curve: Region of interest 1 (ROI central), Red curve: Regions of interest 2 (ROI peripheral) (Color figure online)



	mean		std	
	1	2	1	2
slope_r	1.19	0.84	0.15	0.2
F_{max_r}	13.08	9.34	1.52	1.2
T_{max_r}	11.07	11.42	0.92	1.68
$T_{1/2max\_r}$	5.61	5.73	1.12	1.81
TR_r	0.5	0.49	0.07	0.1

	mean		std	
	1	2	1	2
slope_r	0.85	0.62	0.14	0.1
F_{max_r}	8.93	6.16	0.74	0.4
T_{max_r}	10.67	10.2	1.34	1.55
$T_{1/2max\_r}$	5.43	4.63	1.21	1.45
TR_r	0.5	0.44	0.07	0.1

	mean		std	
	1	2	1	2
slope_r	0.91	0.95	0.05	0.21
F_{max_r}	8.66	10.26	0.98	0.55
T_{max_r}	9.49	11.54	0.89	3.27
$T_{1/2max\_r}$	4.89	5.26	1.17	2.32
TR_r	0.51	0.44	0.08	0.09

Fig. 6 An example of quantitative perfusion measurement and metrics in the ventricle with different camera positions. **A** Camera fixed 7.5 cm from the organ **B** Camera fixed 15 cm from the organ and **C** camera focuses on the periphery of the organ. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

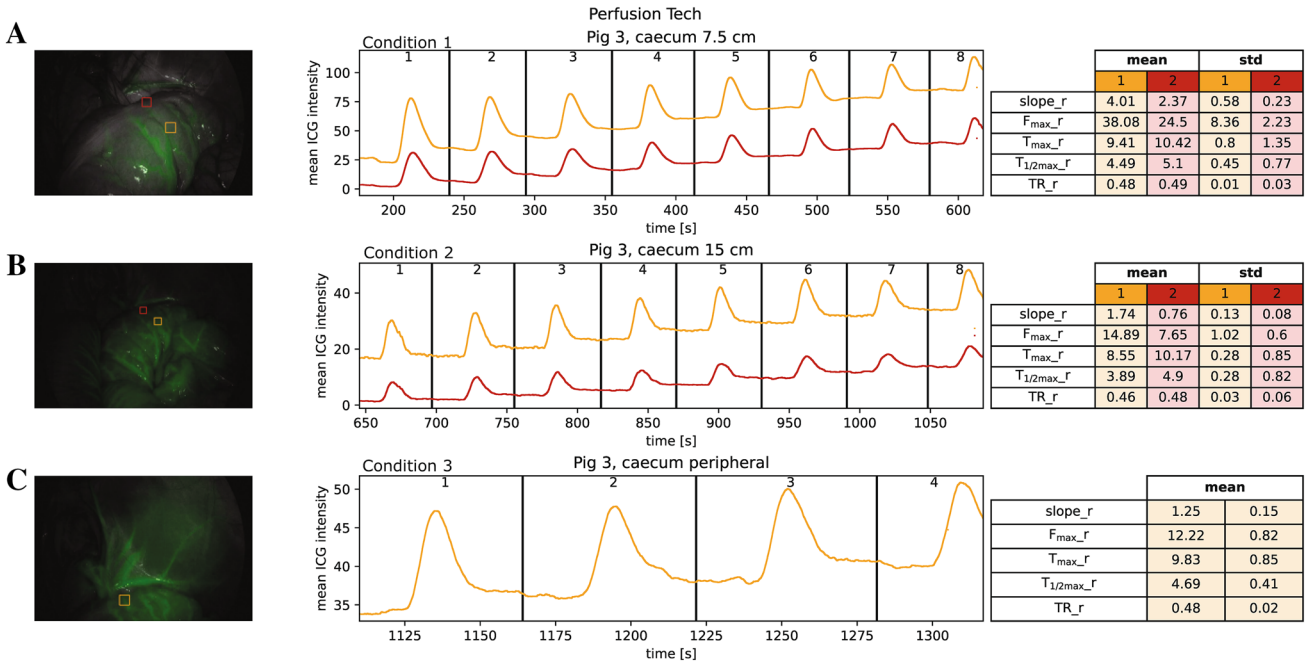


Fig. 7 An example of quantitative perfusion measurement and metrics in the caecum with different camera positions. **A** Camera fixed 7,5 cm from the organ **B** Camera fixed 15 cm from the organ and **C** camera focuses on the periphery of the organ. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

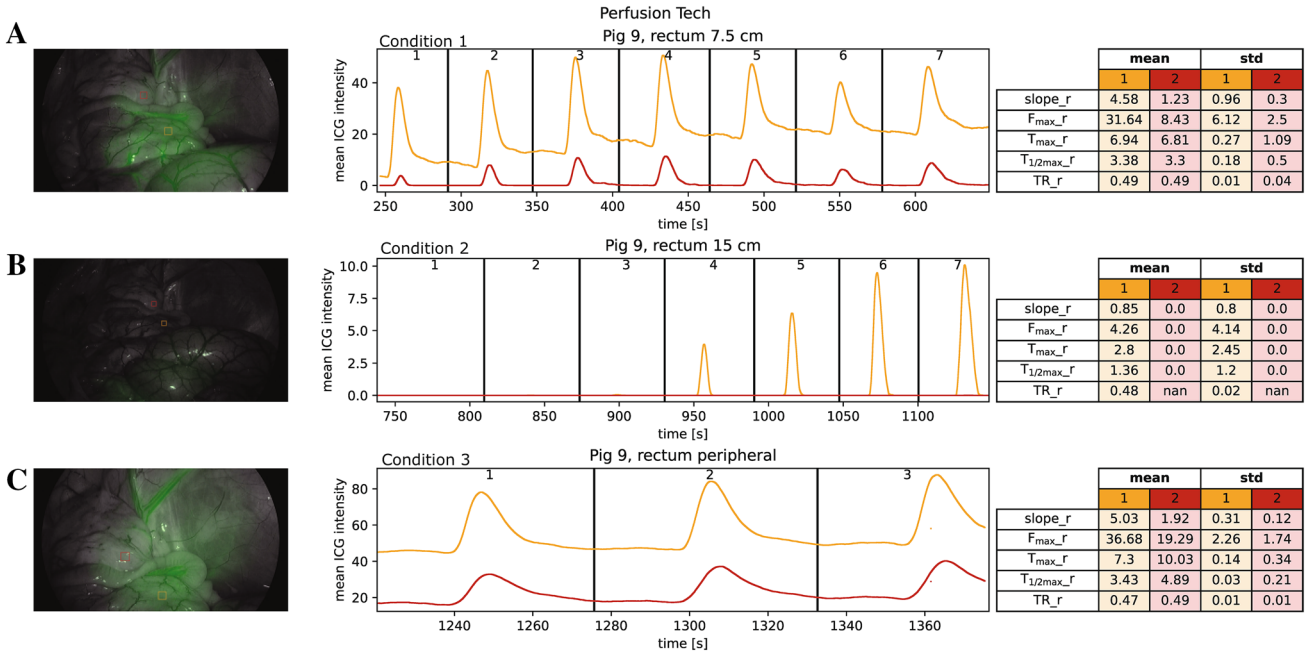


Fig. 8 An example of quantitative perfusion measurement and metrics in the rectum with different camera positions. **A** Camera fixed 7,5 cm from the organ **B** Camera fixed 15 cm from the organ and **C** camera focuses on the periphery of the organ. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

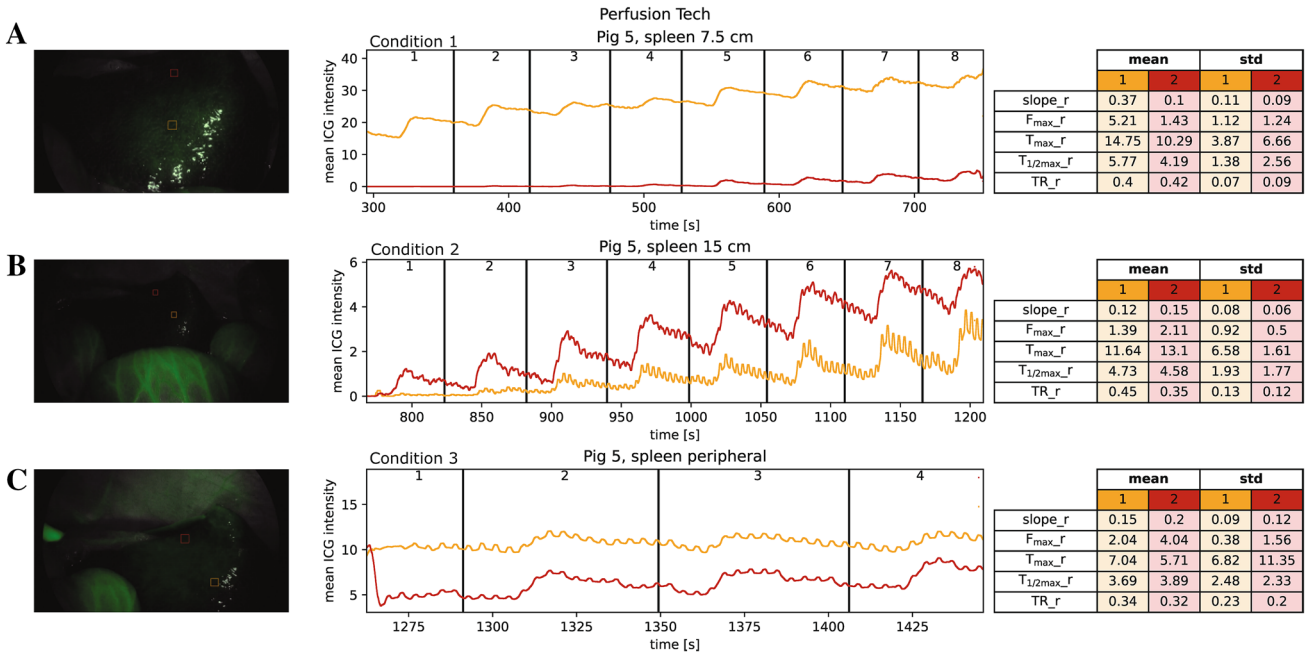


Fig. 9 An example of quantitative perfusion measurement and metrics in the spleen with different camera positions. **A** Camera fixed 7,5 cm from the organ **B** Camera fixed 15 cm from the organ and C – camera focuses on the periphery of the organ. Yellow curve: Region of interest 1 (ROI central), Red curve: Region of interest 2 (ROI peripheral) (Color figure online)

The study has three important limitations. Firstly, this is a proof-of-concept study with the purpose of investigating feasibility of the methodology. Secondly, the study was conducted in an animal model, therefore the result may not be directly transferrable to humans. Due to our small sample size, no conclusions about statistical significance can be made. Thirdly, this experiment was performed using the Stryker 1588 platform, which required switching between white and NIR light between measurements, which limits the possibility of using the methodology as a constant "background surveillance" of the tissue, while performing the surgery. It furthermore necessitated choosing the ROIs retrospectively, due to "cuts" in the video recordings that made continuous ROI tracking throughout all camera conditions impossible. However, other commercially available platforms can now display white and NIR light simultaneously allowing for real-time quantification analysis with minimal surgical interruptions.

The current study is a first step toward developing a novel method of continuous organ perfusion monitoring during abdominal surgery. Noticing changes in perfusion dynamic that otherwise might stay undetected until they manifest as postoperative complications could significantly support surgeons' decision-making, optimize surgical technique, and improve the intra- and postoperative course of the patient. Therefore, future studies assessing the method's ability to distinguish hypoperfused from normoperfused tissue are warranted.

We conclude that quantitative perfusion assessment with a high-frequency, low-dose bolus ICG regimen is feasible in an animal model. Tissue accumulation of ICG over time does not affect the quantification process but further research and software development are needed before the methodology is applicable in the clinical setting.

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Declarations

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