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Evaluation of hyperspectral imaging (HSI) for the measurement of ischemic conditioning effects of the gastric conduit during esophagectomy

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Abstract

Background. Hyperspectral imaging (HSI) is a relatively new method used in image-guided and precision surgery, which has shown promising results for characterization of tissues and assessment of physiologic tissue parameters. Previous methods used for analysis of preconditioning concepts in patients and animal models have shown several limitations of application. The aim of this study was to evaluate HSI for the measurement of ischemic conditioning effects during esophagectomy.

Methods. Intraoperative hyperspectral images of the gastric tube through the mini-thoracotomy were recorded from n=22 patients, 14 of whom underwent laparoscopic gastrolysis and ischemic conditioning of the stomach with two-step transthoracic esophagectomy and gastric pull-up with intrathoracic anastomosis after 3 - 7 days. The tip of the gastric tube (later esophago-gastric anastomosis) was measured with HSI. Analysis software provides a RGB image and 4 false color images representing physiologic parameters of the recorded tissue area intraoperatively. These parameters contain tissue oxygenation (StO_2), perfusion- (NIR Perfusion Index), organ hemoglobin- (OHI) and tissue water index (TWI).

Results. Intraoperative HSI of the gastric conduit was possible in all patients and did not prolong the regular operative procedure due to its quick applicability. In particular, the tissue oxygenation of the gastric conduit was significantly higher in patients who underwent ischemic conditioning ($\overline{StO2}_{Precond.}$ = 78%; $\overline{StO2}_{NoPrecond.}$ = 66%; p = 0.03).

Conclusions. HSI is suitable for contact-free, non-invasive and intraoperative evaluation of physiological tissue parameters within gastric conduits. Therefore HSI is a valuable method for evaluating ischemic conditioning effects and may contribute to reduce anastomotic complications. Additional studies are needed to establish normal values and thresholds of the presented parameters for the gastric conduit anastomotic site.

Keywords

Hyperspectral imaging – gastric conduit – esophagectomy – ischemic conditioning – physiologic tissue parameters

Introduction

Esophago-gastric anastomosis following esophageal resection and gastric pull-up is one of the most complex anastomoses of the gastrointestinal tract with a high potential of insufficiency and consecutive complications, as mediastinitis, pleural empyema, esohago-tracheal (-bronchial) fistula and septic arrosion bleeding (1). This high risk procedure of esophagectomy has been reported in the literature to be associated with a significant morbidity (>40%) and mortality (5-12%) (2,3). During the process of gastric tube formation in the context of esophagectomy, the major blood vessels of the stomach, such as the left gastric artery and vein, the left gastroepiploic artery and vein, as well as the short gastric vessels are divided, with immediate ischemic reaction of the stomach wall. Viability of the gastric conduit then, however, is mostly dependent on the right gastroepiploic arcade. It has been well analyzed by optical fiber spectroscopy (OFS) that oxygen saturation (SaO_2) and blood flow are significantly reduced during this stepwise devascularization of the stomach and that the extent of resulting gastric tube ischemia is associated with clinical outcomes, e.g. anastomotic leaks (4). The stimulus by relative ischemia following division of major vessels, thus, leads to microvascular improvement by neovascularization (5), especially in the later area of the anastomotic site at the tip of the gastric conduit. The concept of preconditioning, including a two-time procedure with an interval of several days to 2-3 weeks between vessel ligation, gastrolysis and gastric tube transposition into the thorax with anastomosis, is well known as ischemic conditioning (delay phenomenon) of the stomach. This method was first described by Urschel in a rat model (6) and further clinically elaborated and laparoscopically applied by Nguyen et al. in a small series of n=9 patients (7), and in the first large retrospective cohort (n=83 patients) by Hölscher et al. (8) and later comparatively by Schröder et al. (n=419; 238 with ischemic conditioning) of the same clinic (9). During the time period between the first and second intervention and the subsequent delayed transposition and esophagogastric anastomosis, the gastric fundus has time to re-establish an abundant blood supply (10). In general, this partial gastric devascularization can technically be performed by open, laparoscopic or robotic surgery. In addition, preoperative radiologic-interventional arterial embolization has been shown to be equally successful (11–16).

Although previous methods used for measuring the effects have shown several limitations and are rather time-consuming, the results of this preconditioning concept have been convincing ever since, demonstrating reduction of anastomotic complications following esophagectomy and gastric pull-up in patients and animal models, due to improved perfusion as well as reduced inflammation and fibrosis at the anastomotic site of the gastric sleeve (8,9,17,18). These parameters are known to be the most important factors for regular healing, apart from tension-free and technically perfect performance of the anastomosis. Animal studies have provided evidence that perfusion was 3 times better at re-intervention after ischemic conditioning, going along with increased vasodilation and angiogenesis, less anastomotic collagen deposition, less ischemic injury, and less muscularis atrophy (19). In clinical studies, especially the severity of anastomotic leakage could be reduced significantly (9,20–22). However, a prospective randomized trial (LOGIC trial = laparoscopic gastric ischemic conditioning prior to minimally invasive esophagectomy) by Veeramootoo et al. failed to show improvement of perfusion at the conduit tip (2). In this study, perfusion of the fundus and the greater curvature of the stomach was recorded by laser Doppler fluximetry, which was validated to assess gastric perfusion by others (23,24). A perfusion coefficient measured as ratio at stage of MIE (minimally invasive esophagectomy) over baseline was used for statistical analysis (2). Others, as the group of Hölscher and Schröder, performed mucosal oxygen saturation (MOS, sulfur dioxide in %) measurements quantitatively from the endoluminal side in well-defined areas of the antrum, corpus and fundus, using a tissue spectrometer located at the tip of a microprobe (8,9,25). In an attempt to search for further reliable methods to assess gastric conduit perfusion, Pham et al. applied optical fiber spectroscopy (OFS) to measure oxygen saturation (SaO_2) and blood volume fraction (BVF) in the distal gastric conduit at baseline and after gastric devascularization, conduit formation, and transposition, with correlation of these readings with clinical outcomes (4). Functional capillary density in ischemic conditioning was assessed by Mittermair et al. in rats in order to investigate time dependent changes of gastric microcirculation by means of intravital fluorescence microscopy (26). Recently, indocyanine green (ICG) fluorescence has been described for evaluating blood supply of the reconstructed tube during esophagectomy (27–29). However, apart from the fact that ICG is an invasive procedure with a considerable rate of cardiovascular complications, comparative studies, regarding the value of ICG in ischemic conditioning of the gastric conduit, are still lacking.

The aim of this study was to evaluate the feasibility of hyperspectral imaging (HSI) for the measurement of ischemic conditioning effects during esophagectomy.

Patients and methods

Only patients who underwent hybrid (abdominal part: minimally-invasive; thoracic part: mini-thoracotomy) or open esophagectomy (n=1 with simultaneous liver resection, see below) could be included, because the used HSI-camera is too large for laparoscopic surgery. Intraoperative hyperspectral images of the gastric tube through the mini-thoracotomy were recorded from n=22 patients (20 males, 2 female) with a median age of 64 (36 - 82) years. Involved were 12 adeno-, 9 squamous-cell carcinomas of the esophagus and 1 reconstruction with gastric pull-up after esophagectomy due to perforation (no carcinoma of the esophagus). In the group of patients undergoing ischemic preconditioning, laparoscopic gastrolysis and ischemic conditioning of the stomach was performed 3-7 days before the operation in n=14 of the 22 patients. In detail, during laparoscopic gastrolysis, first, the lesser omentum close to the lower edge of the liver, then the greater omentum (including the left gastroepiploic artery and vein) is divided, preserving the gastroepiploic arcade. The left gastric artery and vein are clipped and cut centrally, harvesting the lymph nodes of the celiac trunc, and finally, the short gastric vessels are divided up to the left crus. If possible, the right gastric artery and vein are preserved. Kocher's maneuver of the duodenum is carried out and the distal esophagus with the periesophageal lymph nodes is mobilized intrathoracically as far as possible. Patients were sent to the peripheral ward afterwards and could eat a soft diet. The second step of the operation after ischemic conditioning of the stomach consisted of transthoracic esophagectomy via a mini-thoracotomy (in the sense of a hybrid-procedure) with completion of the two-field lymphadenectomy, gastric tube formation by resection of the lesser curvature and adjacent nodes with a linear stapler (from proximal to distal), and intrathoracic end-to-side esophagogastric anastomosis (circular stapler, EEA 25 mm) at the level of the azygos vein.

The decision on whether to perform ischemic conditioning or not was due to the time interval of surgery: After January 1st 2018, we completely changed our concept towards two-step esophagectomies with ischemic gastric preconditioning in general. Conclusively, patients measured before this point in 2017 underwent the single-step esophagectomy without preconditioning. In one patient, simultaneous liver metastatectomy was performed (segment IV) during open gastrolysis and ischemic conditioning of the stomach. All patients underwent intrathoracic anastomosis, except for the gastric tube pull-up reconstruction following esophagectomy, where we performed a cervical esophago-gastric anastomosis. Clinical data of patients are summarized in **Table 1**.

Immediately before construction of the esophago-gastric anastomosis (stapled end-to side, EEA 25 mm circular stapler system) the hyperspectral images were acquired with the TIVITA™ Tissue system (Diaspective Vision GmbH, Am Salzhaff, Germany). This HSI-camera has a push broom scanner providing images with a high spectral resolution (5 nm) in the visible and near infrared range (500-1000 nm). The Number of Effective Pixels is 640 × 480 (x-, y-axis). All measurements were taken at a distance of 30 cm between the object and the camera lens with a focal length of 25 mm. This setup results in a field of view (FOV) of 6.4 × 4.8 cm^2 and a spatial resolution of 0.1 mm/pixel. Illumination is done by 8 halogen spots (20 W each) which are directly integrated in the camera housing. For accurate measurements, the ceiling lights in the operating room were switched off during image recording (approximately 10 seconds). After a computation time of 8 seconds, the analysis software provides a RGB image and 4 false color images that represent physiologic parameters of the recorded tissue area intraoperatively. These parameters contain tissue oxygenation (StO_2), perfusion- (NIR Perfusion Index), organ hemoglobin- (OHI) and tissue water index (TWI). The relative blood oxygenation in the microcirculation of superficial tissue layers (approximately 1 mm) is represented by StO_2 [%], while the NIR Perfusion Index [0-100] represents tissue layers in 4-6 mm penetration depth. The indices OHI [0-100] and TWI [0-100] display the distribution of hemoglobin and water in the observed tissue area, respectively. A detailed description and validation of the parameters can be found in the work of Holmer et al.(30).

The location of the later anastomosis was depicted by a forceps during the measurement **Fig. 1**. The area within the diameter of 25 mm around the marked position is called region of interest (ROI). For each parameter image the index average was calculated from the values inside the ROI.

Data were collected prospective and analyzed retrospective with LabVIEW. Statistics of physiological parameter indices are presented in mean, median, quartiles and p-value. The f-test was performed to check for equal variances and unpaired two-tailed Student's t-test was used to determine statistical significance. The statistical analyses were performed with Microsoft Excel 2013.

Results

Intraoperative hyperspectral imaging of the tip of the gastric tube (later anastomosis) was possible through mini-thoracotomy in all our patients undergoing hybrid or open (n=1 patient with simultaneous liver resection during gastrolysis) esophagectomy. HSI measurements did not prolong the regular operative procedure due to its quick applicability (10 seconds per recording and its almost “real-time” possibility of visualization and interpretation). In particular, HSI enabled to distinguish between gastric sleeves with and without ischemic conditioning: A significantly lower mean oxygenation inside the ROI of the gastric conduit was observed in patients without pretreatment (one-step esophagectomy) ($\overline{\mathrm{StO2}}_{\mathrm{NoPrecond.}}$ = 66%) compared to patients with ischemic preconditioning ($\overline{\mathrm{StO2}}_{\mathrm{Precond.}}$ = 78%; p = 0.03). Even though not significant, differences in organ hemoglobin index ($\overline{\mathrm{OHI}}_{\mathrm{NoPrecond.}}$ = 42; $\overline{\mathrm{OHI}}_{\mathrm{Precond.}}$ = 46;

p = 0.51) and tissue water index ($\overline{\mathrm{TWI}}_{\mathrm{NoPrecond.}} = 59$; $\overline{\mathrm{TWI}}_{\mathrm{Precond.}} = 63$; p = 0.50) were found for both patient groups. Median, lower and upper quartiles of the ROI mean index for each parameter are summarized in **Table 2** and the distribution among the patients is described in **Fig. 2**.

The postoperative course was uneventful in all patients with regular healing and timely oral nutrition following surgery, except for one non-preconditioned patient. This patient developed a small anastomotic leak of the intrathoracic anastomosis without mediastinitis or sepsis on postoperative day 7, which could be managed conservatively using endoscopic vacuum therapy (Endosponge).

Discussion

Our data clearly show for the first time the feasibility and reliability of hyperspectral imaging (HSI) measuring the ischemic conditioning effects of the gastric conduit and the discrimination possibility to non-preconditioning during esophagectomy. Previous methods used for this analysis in patients and animal models have shown several limitations of application and usefulness and are time-consuming.

The studies supporting the concept of ischemic conditioning, including an animal experiment (8,9,17,18), are of non-randomized character. However, the only prospective-randomized trial (LOGIC trial) (2), did not confirm the benefits claimed for ischemic conditioning. This study might have been underpowered and the final endpoint, anastomotic insufficiency, is known to be multifactorial, strongly depending on the surgeon’s technique. A more sophisticated endpoint would have been vascularization of the tip of the gastric tube.

HSI is a relatively new method used in image-guided and precision surgery, which has shown promising results for recognition/characterization of tissues/tumors (31–36), and comprehensive assessment of physiologic tissue parameters, such as perfusion, oxygenation, and water content (37–40). Hence, it has been applied predominantly in wound imaging and -management in plastic surgery transplants, vascular surgery, chronical wounds and burn injuries so far (41–44). In our study group, we were able for the first time to use the system to assess tissue parameters of gastrointestinal anastomoses in visceral surgery *in vivo* (40). HSI, as a contact-free, non-invasive method with no need of contrast medium, provides objective “real time” perfusion-, oxygenation and hydration evaluation of organs and especially of anastomotic sites intraoperatively, which can possibly contribute to determining the “ideal” region of anastomosis with the intent of improved healing (40). HSI-measurements of the gastric conduit during esophagectomy, especially in the context of ischemic conditioning, have not been published so far to our knowledge.

The applied HSI-technology in our current study has a relevant advantage over conventional multispectral camera systems due to its higher spectral and spatial resolution. Furthermore, our HSI-camera provides a higher penetration depth compared to the technology of digital cameras (0-1 mm). Thus, deeper tissue layers can be reached by the HSI-camera.

Optical fiber spectroscopy (OFS) can be used for the assessment of tissue oxygenation during laparoscopic procedures (4,25). However, OFS covers only a small spot (3 mm) and therefore multiple measurement points are needed, which increases the measuring time. The HSI-camera used in this study is able to cover a large FOV (6.4 × 4.8 cm^2) and a wavelength range up to 1000 nm, which enables the additional analysis of tissue water at 960 nm. Other groups determined changes in gastric blood flow with laser Doppler flowmetry, but did not find significant differences between patients with and without ischemic conditioning (2,45). Blood flow cannot be estimated with HSI, but therefore other perfusion-related parameters, like oxygenation and hemoglobin distribution, which seem to be more promising for the analysis of ischemic conditioning effects.

In contrast to the increasingly applied technology of Near-InfraRed (NIR)-fluorescence with ICG, which has especially been used in colorectal surgery to reduce anastomotic complications, as impressively shown by the PILLAR II multicenter study (46), the non-invasiveness of our HSI-technology has to be pointed out. Serious and life-threatening side-effects after intravenous application of ICG, such as anaphylactic shock, drop in blood pressure, tachycardia, dyspnea, and urticaria, have been described and the risk of significant adverse and secondary effects rises in patients with chronic renal failure, up to sudden deaths in very rarely reported cases. A further disadvantage of ICG is the subjective evaluation of the fluorescence-intensity by pure envisioning of the surgeon and, thus, reflects its limitations. A new method, called fluorescence-based enhanced reality (FLER), which uses fluorescence time-to-peak was described by Diana et al. (47–49) and showed promising results regarding quantitative ICG-measurement of bowel perfusion in the animal model.

In addition, providing comprehensive tissue parameters, such as tissue oxygenation (StO_2), perfusion- (NIR Perfusion Index), organ hemoglobin- (OHI) and tissue water index (TWI), it might be a valuable tool to select the “ideal” anastomotic site of the esophagogastric anastomosis, in order to reduce the risk of leakage. This could be carefully concluded, although casuistic only, by one case of our series, who developed anastomotic insufficiency of the intrathoracic esophago-gastric anastomosis. In this patient, the intraoperative measurements were relevantly lower than the others: StO_2 = 41% (Diff. to $\overline{\mathrm{StO2}}_{\mathrm{NoPrecond.}}$ = 25%), NIR Perfusion Index = 40 (Diff. to $\overline{\mathrm{NIR}}_{\mathrm{NoPrecond.}}$ = 22), OHI = 25 (Diff. to $\overline{\mathrm{OHI}}_{\mathrm{NoPrecond.}}$ = 17). In **Fig. 3** the NIR Perfusion Index image of this patient is compared to a case without postoperative anastomotic leak.

The intraoperative measurements are less time-consuming than most other technologies used for assessment of ischemic conditioning effects (about 18 seconds per document), non-invasive, and contact-free. Additionally, they can be technically very easily performed (e.g. by an OR nurse). However, normal and “cut-off” values for gastrointestinal (tubular) organs, especially for different anastomoses, or the “optimal” gastric conduit status (with and without ischemic conditioning), are still to be defined and established, as the technology mainly derives from wound imaging and management. In the latter, e.g. in plastic and vascular surgery, oxygenation of > 50% predicts a good healing of a wound, whereas 30-50% represent a “grey area”, and values of < 30% are associated with worse healing processes in transplants and chronic wounds (50,51). After establishing and generation of normal values and borderline zones of the gastric conduit anastomotic site, the method will be very helpful to determine the best area of perfusion with the optimal constellation of additional parameters, such as oxygenation and edema, in order to avoid postoperative leakages. With regard to the TWI, we found higher values in the group undergoing ischemic preconditioning. This might be due to the fact that patients received additional fluid therapy following laparoscopic gastrolysis and partial devascularization, as some of them displayed signs of minor gastroparesis after this first step of surgery and enteral nutrition was slightly restricted to prevent aspiration events.

The used HSI-system is intended for use in plastic surgery and wound diagnostics. For applications in visceral surgery, according to the manufacturer’s website, some improvements are currently under development or planned for the future. This includes focused illumination with LEDs to light up structures deep in the situs and correct for ambient light during open surgery. This also holds for the automatic estimation of the object distance to get a focused image. A major advance will be a compact HSI-camera, which is suitable for laparoscopic procedures and provides high resolution videos.

The encountered limitations of HSI for measuring the ischemic conditioning effects of the gastric conduit are the missing gold standard for estimating tissue oxygenation, which makes it difficult to compare it with other methods. The time currently needed for hyperspectral data acquisition and parameter calculation is short (18 seconds) but still not yet fully "real time", a minor downside compared to ICG-imaging, which shall be improved in the near future.

Conclusions

Intraoperative HSI during mini-thoracotomy was used for the evaluation of ischemic conditioning effects. Mean tissue oxygenation and hemoglobin related indices at the later anastomosis location were higher in patients with ischemic preconditioning than without. One patient with noticeable lower values developed anastomotic insufficiency. This work demonstrates, that HSI is suitable for contact-free, non-invasive and rapid intraoperative evaluation of physiological tissue parameters within gastric conduits. Therefore HSI is a valuable method for evaluating ischemic conditioning effects and may contribute to reduce anastomotic complications.

Disclosures

Conflicts of Interest: The hyperspectral camera used for the measurements in this publication was developed by Diaspective Vision GmbH. H. Köhler is employee of this company. In the long term, Diaspective Vision has proprietary interest in the development of the camera system resulting in a product for routine clinical use. The clinical tests of the camera have been performed by clinicians (authors 2, 4-8 and 11). B. Jansen-Winkeln, M. Maktabi, M. Barberio, J. Takoh, N. Holfert, Y. Moulla, S. Niebisch, M. Diana, T. Neumuth, S. M. Rabe, C. Chalopin, A. Melzer and I. Gockel have no financial interests and financial arrangements with Diaspective Vision and have received no funding for the measurements and/or preparation of this manuscript. The cameras used during the measurements have been provided by Diaspective Vision.

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Table 1 Patient demographics and tumor histology

	Ischemic preconditioning	
Variables	Yes (n=14)	No (n=8)
Median age [range] in years	63 [36 - 77]	68 [52 - 82]
Sex, n (males : females)	13 : 1	7 : 1
Tumor type		
Adenocarcinoma	7	5
Squamous-cell carcinoma	7	2
None	-	1
Tumor localization		
Lower third of the esophagus	8	4
Lower and middle third	-	1
Middle third	5	2
Upper third	1	-
None	-	1
Neoadjuvant therapy		
Chemotherapy	4	4
Chemo radiotherapy	9	2
Radiotherapy	1	-
None	-	2

Table 1 Statistics of ROI mean index of measured gastric tubes for each parameter

	Ischemic preconditioning		
Parameters Median [lower-, upper quartile]	Yes (n=14)	No (n=8)	P value
Tissue oxygenation (StO_2)	0.78 [0.71, 0.82]	0.69 [0.55, 0.80]	0.03
NIR Perfusion Index	0.68 [0.61, 0.72]	0.62 [0.59, 0.70]	0.22
Organ hemoglobin index (OHI)	0.52 [0.42, 0.57]	0.43 [0.31, 0.49]	0.51
Tissue water index (TWI)	0.63 [0.53, 0.72]	0.55 [0.51, 0.62]	0.50

Fig. 1 RGB image with marked ROI at later anastomosis location (left) and false color image of tissue oxygenation (right).

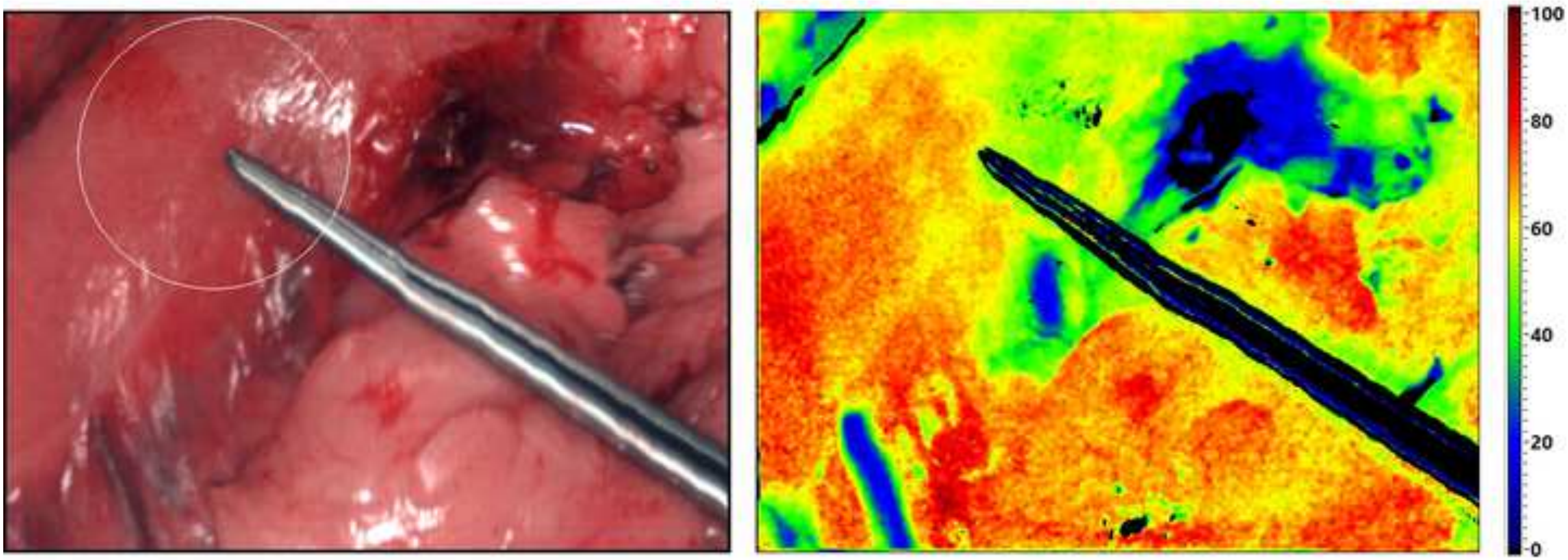

Fig. 3 RGB- and NIR Perfusion Index- images of a patient with (A, B) and without postoperative anastomotic insufficiency (C, D).

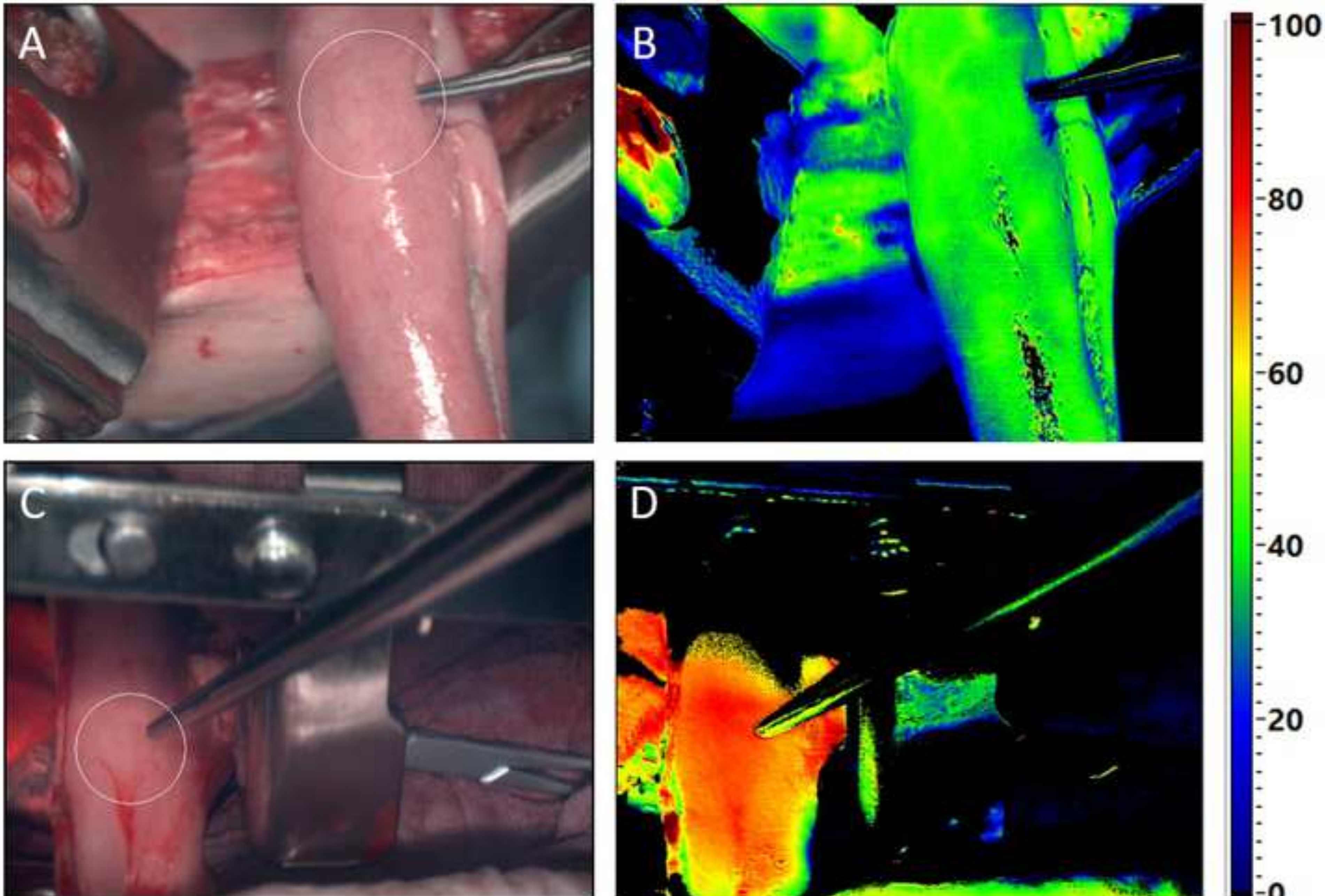

Fig. 2 Distribution of the index average inside the ROI among patients with and without ischemic preconditioning for a) tissue oxygenation (StO2), b) perfusion- (NIR Perfusion