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Imaging Photoplethysmography for Noninvasive Anastomotic Perfusion Assessment in Intestinal Surgery

Stefan D. van der Stel, MD,[a,b,1,*] *Marco Lai, MSc,*[c,d,1] *Harald C. Groen, PhD,*[b] *Mark Witteveen, MSc,*[a,b] *Koert F.D. Kuhlmann, MD, PhD,*[b] *Brechtje A. Grotenhuis, MD, PhD,*[b] *Niels F.M. Kok, MD, PhD,*[b] *Mark van Gastel, PhD,*[d,e] *Benno H.W. Hendriks, PhD,*[c,f] *and Theo J.M. Ruers, MD, PhD*[a,b]

[a] *Faculty TNW, Group Nanobiophysics, Twente University, Enschede, The Netherlands*
[b] *Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands*
[c] *IGT & US Devices & Systems, Philips Research, High Tech, Eindhoven, The Netherlands*
[d] *Eindhoven University of Technology, Department of Electrical Engineering, Eindhoven, The Netherlands*
[e] *Patient Care & Monitoring, Philips Research, Eindhoven, The Netherlands*
[f] *Biomedical Engineering, Delft University of Technology, Delft, The Netherlands*

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ABSTRACT

Introduction: Anastomotic leakage after gastrointestinal surgery has a high impact on patient's quality of life and its origin is associated with inadequate perfusion. Imaging photoplethysmography (iPPG) is a noninvasive imaging technique that measures blood-volume changes in the microvascular tissue bed and detects changes in tissue perfusion.

Materials and methods: Intraoperative iPPG imaging was performed in 29 patients undergoing an open segment resection of the small intestine or colon. During each surgery, imaging was performed on fully perfused (true positives) and ischemic intestines (true negatives) and the anastomosis (unknowns). Imaging consisted of a 30-s video from which perfusion maps were extracted, providing detailed information about blood flow within the intestine microvasculature. To detect the predictive capabilities of iPPG, true positive and true negative perfusion conditions were used to develop two different perfusion classification methods.

Results: iPPG-derived perfusion parameters were highly correlated with perfusion—perfused or ischemic—in intestinal tissues. A perfusion confidence map distinguished perfused and ischemic intestinal tissues with 96% sensitivity and 86% specificity. Anastomosis images were scored as adequately perfused in 86% of cases and 14% inconclusive. The cubic-Support Vector Machine achieved 90.9% accuracy and an area under the curve of 96%. No anastomosis-related postoperative complications were encountered in this study.

* *Corresponding author*. Department of Surgical Oncology, Antoni van Leeuwenhoek hospital, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands. Tel.: +31 20 512 3465.
E-mail address: s.vd.stel@nki.nl (S.D. van der Stel).
[1] These authors contributed equally to this work.
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Conclusions: This study shows that noninvasive intraoperative iPPG is suitable for the objective assessment of small intestine and colon anastomotic perfusion. In addition, two perfusion classification methods were developed, providing the first step in an intestinal perfusion prediction model.

Introduction

Anastomotic leakage (AL) is a serious postoperative complication in gastrointestinal surgery with a prevalence that ranges between 1% and 19%, depending on patient-specific risk factors and the anatomical site of the anastomosis.[1,2] Multiple causes are known to lead to AL, of which inadequate vascular perfusion is most significantly correlated.[3,4] Currently, surgeons assess perfusion of the anastomosis by visual inspection of tissue color and by tactile feedback of pulsations in the mesentery, but both methods are susceptible to misinterpretations.[5]

Intraoperative detection of ischemia in the anastomosis has been a long researched clinical topic. Multiple techniques are being explored for objectively assessing organ perfusion in a surgical setting, such as visual grading systems,[2] fluorescence imaging,[6] and hyperspectral imaging (HSI).[7] Despite showing promising results, these techniques are limited by the lack of direct assessment of the mucosal vasculature (visual grading system) or the dependence of injection of contrast agents (fluorescence imaging). Recently, a large study with HSI in anastomosis perfusion assessment showed valuable results toward intraoperative use.[7] However, the main limitation for HSI is the necessity for technological improvements such as real-time video imaging and a laparoscopic HSI camera, before a widespread introduction can be achieved. Thus, an objective measure which is clinically accepted for assessing intraoperative tissue perfusion is yet to be introduced.

Imaging photoplethysmography (iPPG) is a noninvasive optical technique that measures blood-volume changes in the microvascular tissue bed beneath the organs' surface. In the past, iPPG has proven to be highly sensitive and able to detect even slight perturbations in tissue perfusion.[8,9] iPPG brings multiple advantages to the surgical setting, being both noninvasive and having a short acquisition time of 15-30 s, allowing for near real-time feedback. Recent studies showed the capacities of iPPG in both experimental and clinical settings.[10-12] Moreover, an analytic model was developed to determine intestinal perfusion by iPPG.[10] Color-coded perfusion maps extracted from iPPG acquisition were able to display intestinal perfusion in detail.

The aim of this study is to evaluate the clinical performance of iPPG in open gastrointestinal surgery by assessing intestinal perfusion in different perfusion conditions during surgery in a larger patient sample. iPPG acquisitions of the anastomosis were correlated with postoperative outcomes and a qualitative assessment was defined that eventually could be used as a guide for bowel perfusion and AL risk.

Methods

Study population

During 18 mo (between June 2020 and November 2021), in total 29 patients were included in the Antoni van Leeuwenhoek Hospital (Amsterdam, the Netherlands) that underwent surgical segment resection of the small intestine or colon by laparotomy. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute (AVL-NKI) and registered with number IRBd19-155. Inclusion criteria were age $>$ 18 y and a surgical procedure conducted by laparotomy. A written informed consent for participation was provided by all patients included in the study. Data were acquired as per the Institutional Review Board guidelines of the Antoni van Leeuwenhoek Hospital.

Data collection

The iPPG camera setup used in this study is described in detail in our previous work.[10] In short, the setup consisted of an off-the-shelf 2.8-Megapixels RGB camera (Manta G283 B, Allied Vision Technologies GmbH, Germany) with a 52-mm objective and an LED ring in the visible range (Falcon Eyes Macro ringlight MRC-80FV, Benèl BV, the Netherlands) equipped with a cross-polarized light filter (Edmund Optics, Visible linear polarizer). The camera, mounted on a tripod, was used to acquire videos at 20 frames per sec with 12-bit color depth. For optimal focus, the iPPG setup was positioned approximately 50 cm from the target tissue. Exposure time and color gain were adjusted to maximize the light that hits the camera sensor, which contains the actual PPG signal originating from the tissue. During surgery, three videos of 30 s each were acquired, each displaying distinct phases of the surgical procedure and associated perfusion conditions, which were identified by an experienced gastrointestinal surgeon. First, a healthy part of the intestine was imaged ("perfused"). Next, the vasculature was ligated of the part of the intestine which was going to be excised and the ischemic intestine was imaged ("ischemic"). Ischemia was confirmed by visual color changes of the tissue and lack of palpable pulsations. Imaging was performed within 5 mins after blood vessel ligation. When possible, fully perfused intestines were imaged with adjacent ischemic parts from which the supplying vasculature in the mesentery was ligated. Finally, the anastomosis was imaged ("anastomosis").

Data analysis

Data were processed offline in Matlab (R2021b, the Mathworks Inc, Massachusetts) using a custom-built script.[10] This

allowed for manually selecting regions of interest (ROI) of the video, as such that only the intestine was analyzed by the software. Video stabilizing ensured that each pixel measures the same portion of the intestine over time as much as possible, enhancing the PPG signal contained in each pixel of the video. Perfusion maps were generated from the videos and several iPPG-derived perfusion parameters were extracted: amplitude map, delay map, and the signal-to-noise ratio (SNR). The iPPG amplitude map displayed flow of blood in tissues and was expressed as the median due to the lack of a normal distribution in the amplitude map. The iPPG delay map displayed the iPPG arrival time in the recorded area. Perfused tissue was defined where the pulsatility arrives simultaneously throughout the imaged tissue and was represented with a uniform color that is close to 0 s. On the other hand, ischemic tissues experienced increased delay times in pulsatility arrival, leading to a random distribution of arrival times in the delay map. For the delay map, the interquartile range (IQR) was used due to its characteristics to provide information about the spread within the delay map, thereby eliminating extreme outliers caused by inherent noise. SNR was defined as the ratio between the true PPG signal and random noise and provides additional information about the reliability of perfusion assessment. Together, the amplitude and delay maps provide a reliable representation of the clinical situation.[10]

Perfusion classification and confidence models

Two types of classifications were applied for comparing the perfusion conditions and subsequently define a differentiation between perfused and ischemic tissues; a perfusion confidence map for easy representation and a cubic-Support Vector Machine (SVM) for a binary classification. For the perfusion confidence map, the amplitude and the delay were combined into a single predictor variable. The predictor for the model was the angle between the amplitude and delay. Perfused acquisitions were considered as true positive perfusion conditions and ischemic acquisitions as true negative perfusion conditions. A perfusion confidence map was generated to evaluate between perfused and ischemic measurements with a 95% confidence interval (CI). When acquisitions were located outside the CI, the perfusion state cannot be confidently determined and can either be perfused or ischemic ("inconclusive"). In addition, a cubic-SVM was trained to assess anastomosis acquisitions. The cubic-SVM used both the amplitude and the delay as features for the classification. The cubic-SVM had a binary output, labeling the anastomosis as "perfused" or "ischemic". Five-fold cross-validation was used to protect against overfitting.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics v27 (SPSS Inc, Chicago) and Matlab (R2021b, the Mathworks Inc, Massachusetts). Quantitative data are presented as means and standard deviations, whereas qualitative data are presented as numbers and percentages. Normal distribution was assessed with the Shapiro–Wilk test. Statistical analysis was performed using a two-way analysis of variance followed by post hoc pairwise comparison with Bonferroni correction for normal distributed data; the Wilcoxon signed-rank test was performed for non-normally distributed data. A P value ≤ 0.05 was considered statistically significant. Model classification performance was assessed with the receiver operating characteristic curve with the outcome measurements sensitivity, specificity, accuracy, and area under the curve.

Results

General data

In total, 29 patients' baseline characteristics are shown in Table 1 undergoing segment resection of the small intestine (51.7%) or colon (48.3%) were included. In the majority of patients, a side-to-side anastomosis was created to restore the continuity (86.2%). In one case, there was no anastomosis because ultimately there was no resection performed (open-close procedure).

iPPG-derived perfusion parameters

For all patients, perfused intestines were imaged, whereas for 28 of 29 patients, acquisitions of ischemic intestines and the anastomosis were obtained. Small intestine and colon tissues were analyzed individually and pooled for statistical analysis (Fig. 1). iPPG signal amplitude and SNR were distributed normally ($P > 0.05$), whereas the IQR of the delay map was not distributed normally ($P < 0.05$). The iPPG amplitude was correlated with perfusion of the tissue (Fig. 1A). The amplitude for fully perfused tissues and the anastomosis were closely

Table 1 – Patient demographics.

Number of patients	29
Gender, *n*	
Male	12
Female	17
Age, years, mean ± SD	61 ± 10
Preoperative neoadjuvant therapy, *n*	
NACT	7
No preoperative therapy	22
Type of surgery, *n*	
Small intestine resection	15
Colon resection	14
Right hemicolectomy	9
Transversectomy	1
Left hemicolectomy	1
Sigmoid resection	3
Anastomosis type, *n*	
Side-to-side	25
Side-to-end	3
No anastomosis	1

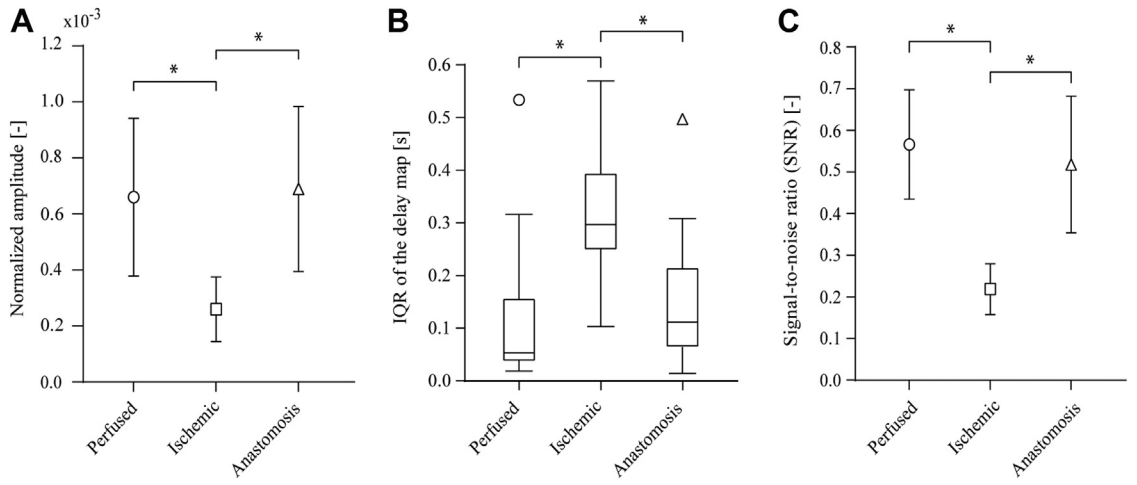

Fig. 1 – (A) Normalized intensity of the iPPG amplitude shows high values in perfused tissues, whereas values are low in ischemic conditions. (B) The IQR of the delay maps follows an inversely correlated trend with low levels of variation in the delay map in perfused conditions and high delay in ischemic conditions. (C) Similar to the iPPG amplitude, the signal-to-noise ratio (SNR) is high in perfused tissues and low in ischemic tissues. (A) and (C) Values are expressed as mean ± standard deviation, (B) values are expressed as median, lower/upper quartiles and min/max; *P ≤ 0.0001.

related, whereas for ischemic tissues the amplitude was much lower. IQR of the delay map was inversely correlated with tissue perfusion. The variation of the delay map was low in perfused conditions and high in ischemic tissues (Fig. 1B). The SNR was, similar to the amplitude, correlated with intestinal perfusion (Fig. 1C).

Perfusion assessment with iPPG

During surgery, ischemic intestines were imaged alongside healthy intestines (Fig. 2A). After acquisition and analysis, amplitude and delay maps were generated and overlaid onto the intraoperative image. The iPPG amplitude map displays

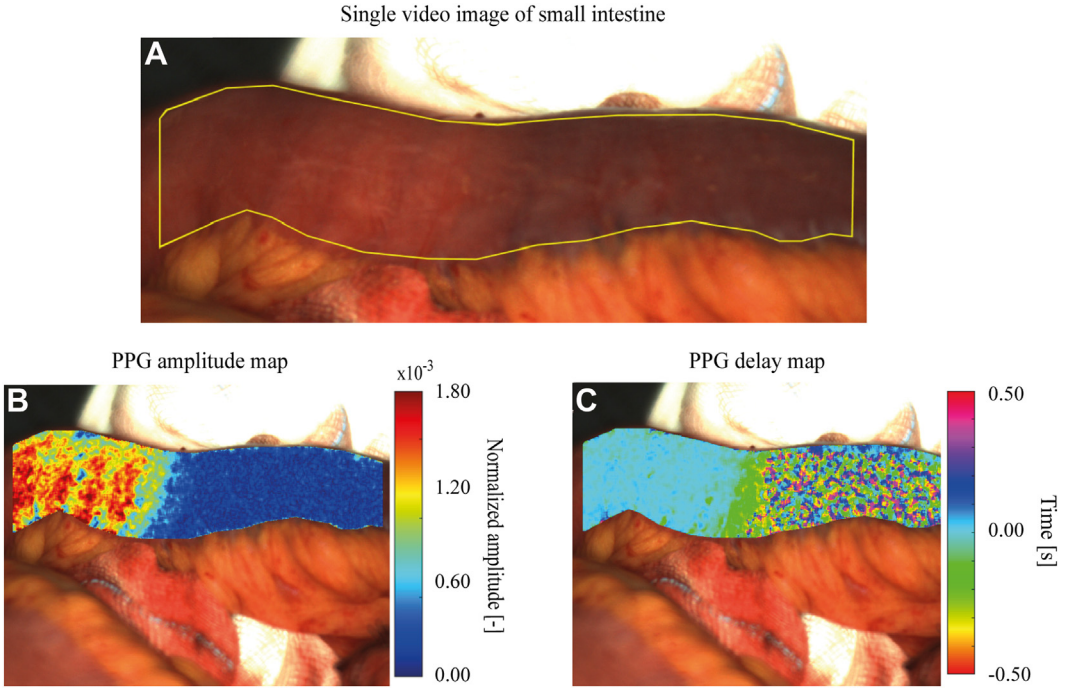

Fig. 2 – Intraoperative iPPG acquisition and analysis. (A) Intraoperative situation presented by the surgeon where the vasculature of the right part of the intestine that is going to be excised is dissected but the continuity of the intestines is still intact. The intestine area on the left is fully perfused. (B) The iPPG amplitude map displays high signal intensity in the fully perfused tissue (normalized amplitude $> 0.6 \times 10^{-3}$), whereas ischemic areas have much lower intensity (normalized amplitude $< 0.2 \times 10^{-3}$). (C) iPPG delay time is uniform in fully perfused tissues (delay time close to 0 sec), whereas delay time displays large variations of ± 0.2 s in ischemic tissues.

high signal amplitude in the fully perfused, healthy intestine, and very low signal amplitude in the ischemic intestine (Fig. 2B). For this case, the normalized iPPG amplitude map values were between 0.00 and 1.80 $\times$ 10^{-3}. For the delay map, a random signal pattern was present with large variations in delay more than $\pm$ 0.2 s in the ischemic intestine, whereas the perfused intestine had a uniform distribution of the signal (Fig. 2C).

A close-up of the perfusion conditions with both perfused and ischemic intestinal parts is shown in Figure 3. Perfused (green ROI) and ischemic (red ROI) intestinal regions are separated by a transition zone (yellow ROI, Fig. 3A). The amplitude map of a fully perfused intestinal region displays a high signal intensity (Fig. 3B), whereas this is much lower after ligation of the intestine vasculature (Fig. 3D). In the transition zone, a demarcation can be observed where perfusion levels change (Fig. 3C). For the delay map, a fully perfused intestinal part is characterized by a uniform signal (Fig. 3E). Oppositely, when perfusion is absent, the delay map displays a random distribution of the signal with high delays in blood flow (Fig. 3G). In addition, in the transition zone, a shift can be observed from high variation in delay time in tissues with ligated vasculature to low variability in delay time in fully perfused tissues (Fig. 3F).

After excision of the ischemic intestine, the newly formed anastomosis was imaged immediately (Fig. 4A). iPPG amplitude levels are high in the imaged ROI of the anastomosis; however, differences in amplitude are observed between the proximal and distal ends (Fig. 4B) were observed in the majority of cases. However, this phenomenon was distributed randomly and no trend was detected for which end displayed higher iPPG amplitude levels, in either small intestine or colon.

Predictive value of iPPG

A perfusion confidence map (Fig. 5A) was used to determine the predictive capabilities of iPPG in assessing anastomosis perfusion (Fig. 5B). The upper bound of the map (green area) describes the values at which the model has a 95% confidence that the tissue in that acquisition is perfused. Similarly, the lower bound of the map (red area) describes the values at which the model has a 95% confidence that the tissue is not perfused. The CI (yellow area) is an indication that the model is not confident, below 95% confidence, that the tissue is perfused or not perfused. The perfusion confidence map achieved 96% sensitivity and 86% specificity for the shown threshold (Fig. 5A). Next, the trained model was compared to anastomosis acquisitions with a known clinical outcome—AL or not—to verify the performance of the model on unseen data (Fig. 5B). Most of the anastomosis acquisitions were located above the upper bound of CI, with five acquisitions located within the CI (inconclusive) and none located below the lower bound of CI. Afterward, the cubic-SVM was given the

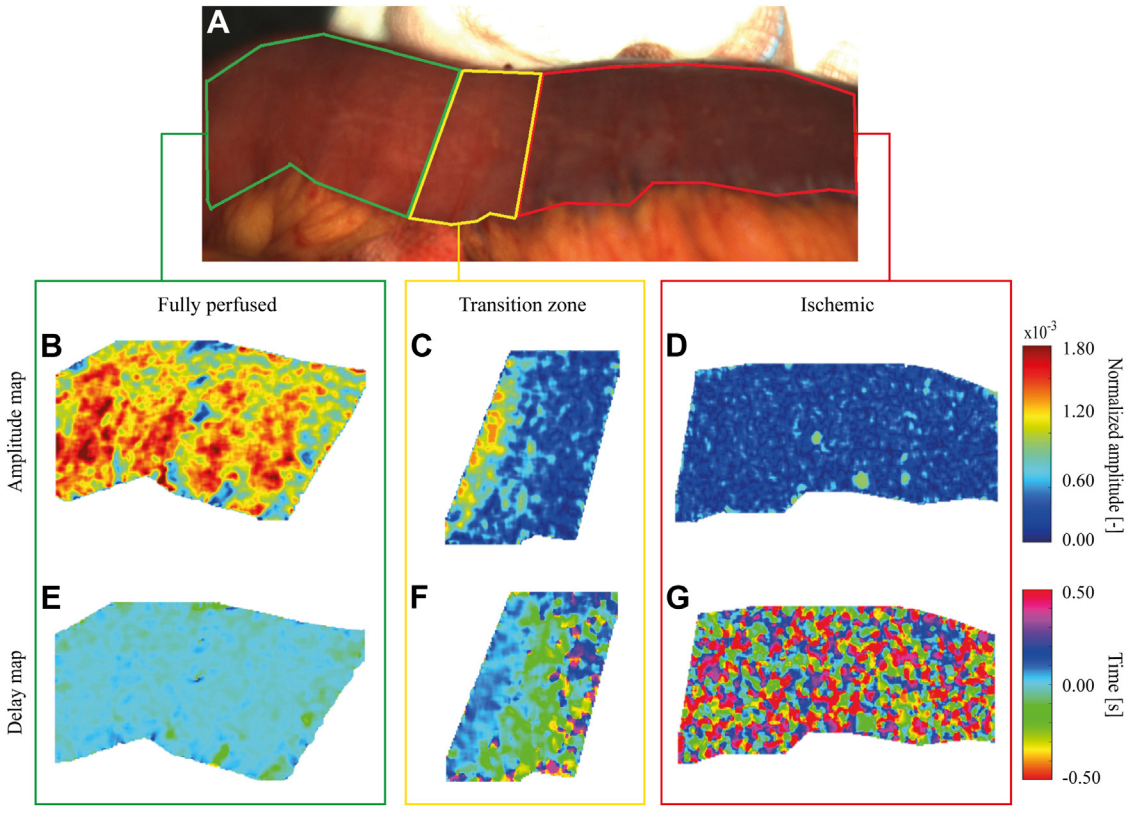

Fig. 3 – Close-up of different perfusion conditions during surgery. (A) Intraoperative situation with isolated areas of perfusion (green ROI), transition zone (yellow ROI), and ischemia (red ROI). iPPG amplitude maps (B-D) and iPPG delay maps (E-G) display characteristic maps in accordance with perfusion levels. (C,F) The transition zone displays a clear transition between perfused and ischemic intestines.

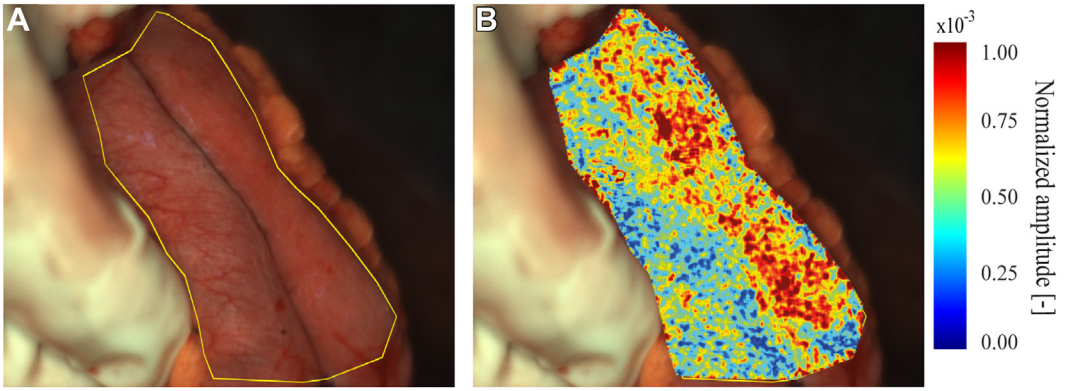

Fig. 4 – Perfusion assessment of side-to-side intestinal anastomosis. (A) Intraoperative situation with newly formed anastomosis in which the ROI is identified (yellow contour). (B) iPPG amplitude levels extracted from the intraoperative image and overlaid with the RGB image. Perfusion is present in both ends of the anastomosis; however, a higher amplitude is achieved in the right part.

anastomotic measurements. The cubic-SVM predicted "ischemic tissue" near the anastomosis in four cases, whereas these were identified by the perfusion confidence map as "inconclusive". The cubic-SVM reached an accuracy of 90.9% and an area under the curve of 96%, for which the receiver operating characteristic curve is shown (Fig. 6).

Discussion

The present study demonstrates the results of novel iPPG-acquired intestinal perfusion assessment in a surgical setting. Measurements were performed on intestines with different perfusion conditions: fully perfused and ischemic intestines and the newly formed anastomosis. Color-coded perfusion maps generated from iPPG measurements displayed detailed information about perfusion levels. From those maps, extracted iPPG-derived perfusion parameters (amplitude, delay time, and SNR) were highly correlated with tissue perfusion (perfused or ischemic).

iPPG amplitude maps provide detailed information about the perfusion status of the tissue and are easily interpretable by clinicians. For example, a transition zone between perfused and ischemic intestines can be observed when the vasculature is ligated, which can be used as a guide for the surgeon in identifying the ideal resection plane. Moreover, iPPG-derived perfusion parameters displayed similar trends in perfused and anastomosis conditions (Fig. 1), suggesting that perfusion in tissues with intact vasculature rebounds very quickly after extensive manipulation during surgery. After completion of the anastomosis, variable iPPG amplitude values in the proximal and distal ends were observed in majority of patients. However, no clear trend was observed whether the proximal or distal end displayed higher iPPG amplitude levels. Redistribution of blood flow in the remaining intestinal vasculature could explain this phenomenon. When a portion of the

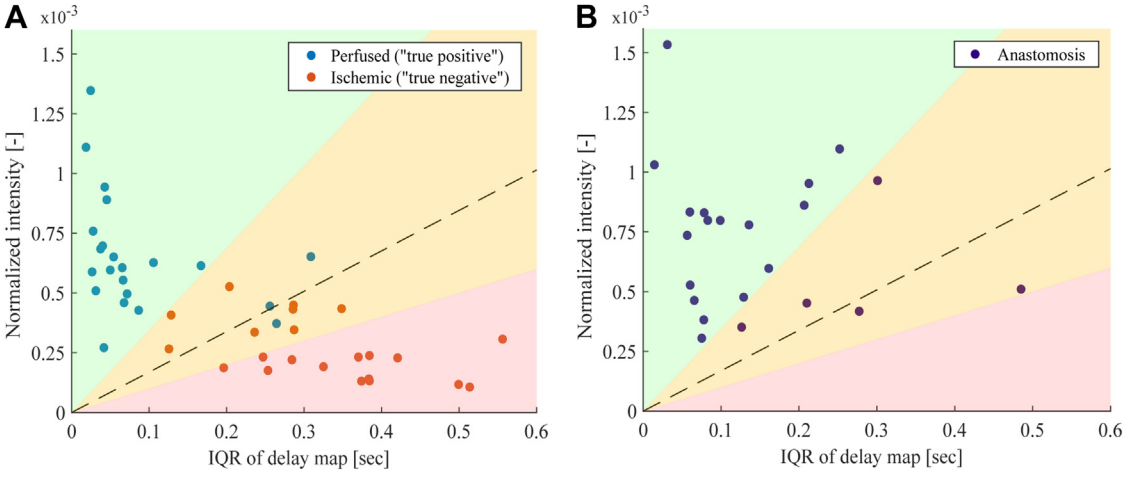

Fig. 5 – Perfusion model. (A) Perfused (true positives) and ischemic (true negatives) acquisitions are used to train a classifier to quantify perfusion conditions in intestinal tissues. The red and green areas represent the area in which the classifier has at least a 95% confidence in the perfusion condition of the assessed tissue. The model has less than 95% confidence in the perfusion condition in the yellow area. (B) Anastomosis acquisitions are plotted with the trained model, with unseen data for the model. Majority of the patients are located within the green area, with five located in the yellow area.

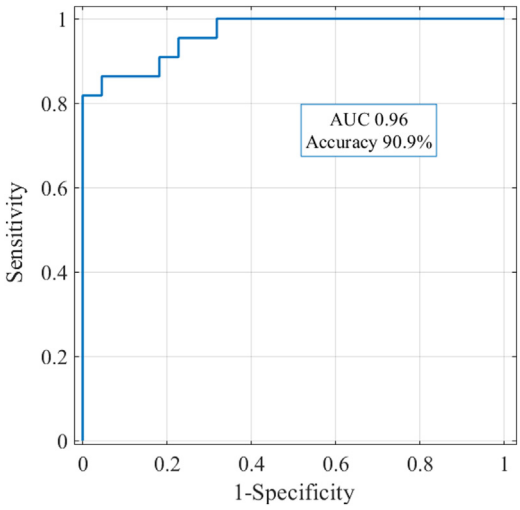

Fig. 6 – ROC for the cubic-SVM using 5-fold cross validation. The ROC curve shows that the cubic SVM is capable of distinguishing between perfused and ischemic intestinal tissues with an AUC of 96%.

intestines is resected, the mesentery with draining lymph nodes and vasculature are simultaneously excised. As a result, redistribution of blood flow in the new vascular anatomy can cause higher flow and pressure in vessels toward one end of the anastomosis compared to the other end.

Despite small variations within patients, interpatient differences were more profound, as shown by the standard deviations in Figure 1. As a result, baseline perfusion measurements are required for assessing anastomosis perfusion per patient. To provide a solution for this problem, two perfusion classification methods were developed using perfused and ischemic perfusion conditions as ground truths. The main advantage of these methods is the possibility for immediate labeling of iPPG measurements during surgery and direct feedback for the surgeon about anastomosis perfusion. In addition, when trained on a large dataset, a generalized model for use in every intestine surgery can be developed. In the present study, after training on ground truths perfusion conditions, the perfusion confidence map achieved 96% sensitivity and 86% specificity. Currently, this model did not show any clear ischemic anastomosis, matching with known clinical outcomes. On the other hand, the cubic-SVM method incorrectly predicted ischemic tissue at the anastomosis area in four cases, ultimately leading to an accuracy of 90.9%. To conclude, the confidence perfusion map can be used as a guide for the surgeon to assess perfusion levels, whereas the cubic-SVM labels the tissue—perfused or ischemic—based on the ground truths.

Although anastomosis-related postoperative complications were absent, anastomosis measurements labeled inconclusive should be carefully evaluated by the surgeon. Due to the uncertainty in the model, these measurements can be either perfused or ischemic. The uncertainty by the model can be caused by factors known for influencing intestinal perfusion, such as drug administration and volume management during surgery and cardiovascular conditions. Effects of these factors on iPPG outcomes should be investigated in further studies. In this study, all inconclusive labeled anastomosis had good clinical outcomes, meaning there were no signs of AL. Thus, a limitation of this study is the observation that no anastomosis-related postoperative complications were recorded. To evaluate iPPG in full extent, a significantly larger study with different surgical outcomes, including patients who develop AL, is required.

Presently, certain anatomical sites—such as colorectal anastomosis—are inaccessible for iPPG acquisition. The current setup with the camera located on a tripod is limited in a way that only allows imaging of intestinal tissues that can be presented to the field of view of the camera. However, when the anatomical location is deep in the pelvic area or the surgical procedure is performed minimal invasively, the current setup is unable to visualize the anastomosis. Especially colorectal anastomoses are of extra interest as they have an AL rate ranging between 5% and 19%.[1] To address this issue and meet the requirements for a minimal invasive surgical setting, iPPG needs optimization for use in minimal invasive surgery. This brings additional challenges, such as implementing iPPG in a laparoscopic system, eliminating surface reflections that are commonly found during laparoscopic procedures, maintaining focus on the region of interest for the duration of the acquisition, fast video recordings, and video stabilization. Nonetheless, when these challenges are overcome, laparoscopic iPPG could be valuable in assessing colorectal and esophageal anastomosis in the minimally invasive setting.

iPPG brings several advantages compared with other perfusion assessment techniques. First, iPPG is a noninvasive technique that does not require administration of fluorophores or contact with the patient, which are key features in fluorescence imaging with ICG or laser Doppler. iPPG is a low-cost and simple technique with a shallow learning curve for operating the setup, which is in contrast with HSI. Because there is no need for technical assistance, iPPG can be easily implemented in the workflow of surgeons and scrub nurses. Second, iPPG is very accurate in detecting intestinal vasculature, which is located in the submucosal layer.[13] Based on the penetration depth of 2-4 mm of iPPG in the intestinal wall, and wall thickness in small intestines (3-5 mm)[14] and colon (1-5 mm),[15] iPPG can accurately assess intestinal perfusion without interference of the lumen or intestinal tissues opposite of the lumen circumference. Finally, iPPG can be used in situations when patients suffer from cardiac arrhythmias. Recent studies have shown that iPPG is able to detect cardiac arrhythmias such as atrial fibrillation,[16] tachycardia, bradycardia, and ventricular tachycardia with a true positive rate of 93%.[17] Being able to detect these cardiac arrhythmias improves the accuracy of iPPG and allows for compensating for arrhythmias in the analysis.[18]

In conclusion, iPPG is an accurate and simple technique that proved to be a promising approach for accurately detecting perfusion in the small intestine and colon microvascular tissue bed with a single, noninvasive acquisition. Perfusion parameters were extracted from intraoperative iPPG recordings of perfused and ischemic intestinal tissues, and the anastomosis, displaying accurate correlation with perfusion conditions. With these results, the first step to determine the predictive capacities of iPPG for discriminating between

good and inadequately perfused intestinal regions has been acquired.

Author Contributions

Study design: T.J.M.R. and B.H.W.H. Data collection: S.D.v.d.S., H.C.G., K.F.D.K., B.A.G., N.F.M.K., and T.J.M.R. Data interpretation: S.D.v.d.S., M.L., H.C.G., M.W., M.v.G., B.H.W.H., and T.J.M.R. Writing manuscript: S.D.v.d.S., M.L., H.C.G., and M.W. Reviewing manuscript: K.F.D.K., B.A.G., N.F.M.K., M.v.G., B.H.W.H., and T.J.M.R.

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Disclosure

None declared.

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Data Accessibility

The datasets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on a reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the hospital's intuitional review board and a written informed consent was provided by each patient included in this study.

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