

Real-time intraoperative detection of tissue hypoxia in gastrointestinal surgery by wireless pulse oximetry

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Abstract

Objective Dehiscence or leakage after bowel anastomoses is associated with high morbidity and mortality. Perfusion and local tissue oxygenation (StO_2), independent of systemic oxygen saturation, are fundamental determinates of anastomotic viability. Because current technology is limited for monitoring local StO_2 at bowel anastomoses, our goal was to construct a wireless pulse oximeter (WiPOX) to monitor real-time intraoperative tissue oxygenation, permitting identification of compromised anastomotic perfusion.

Methods We have: (a) designed a handheld device capable of real-time monitoring of serosal and mucosal StO_2 through endoscopic ports with wireless data transmission to standard intraoperative monitors, (b) constructed the WiPOX using materials meeting FDA regulations for intraoperative use and reuse, (c) performed accuracy testing in humans by comparing the WiPOX to standard pulse oximeters, and (d) tested WiPOX efficacy for detecting early tissue hypoxia in stomach, intestines, and kidneys in anesthetized rats and swine.

Results In humans, WiPOX demonstrated accuracy within 3% compared with commercially available pulse oximeters.

Application of the WiPOX in rats and swine demonstrated normal serosal and mucosal StO_2 and pulse rates in healthy small bowel and stomach. Within 30 s of compromised perfusion, the WiPOX detected bowel hypoxia over a wide range of oxygen saturation ($p < 0.005$). A greater degree of hypoxia was detected in mucosal versus serosal measurements during early ischemia, despite normal appearance of tissue. The onboard sensor-processor unit permitted noninvasive pulse oximetry and integration with current intraoperative monitoring. The contact pressure-sensing head allowed for consistent, high-quality StO_2 waveform readouts despite the presence of body fluids.

Conclusions We have constructed, validated, and successfully tested a novel wireless pulse oximeter capable of detecting intraoperative tissue hypoxia in open or endoscopic surgery. This device will aid surgeons in detecting anastomotic vascular compromise and facilitate choosing an ideal site for bowel anastomosis by targeting well-perfused tissue with optimal healing capacity.

Keywords Anastomotic leak · Tissue oxygenation · Bowel hypoxia · Oximetry

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Anastomotic complications after gastrointestinal (GI) surgery are associated with substantial postoperative morbidity and mortality representing a significant healthcare burden. Specifically, anastomotic leak is associated with decreased survival after GI surgery [1, 2]. Anastomotic leak is identified following 0–50% of esophageal resections and reconstructions with an associated mortality of 35% [3–5]. Leakage from the pancreaticojejunral anastomosis, which complicates up to 20% of pancreatic anastomotic operations, results in a 5–10% mortality rate [6, 7]. Similar outcomes are noted with colonic and small bowel

operations [8]. Morbidity is significant even in survivors, who often require multiple reoperations, extended length of hospital stay, and decreased overall quality of life [2, 9, 10]. In particular, anastomoses after rectal surgery are at high risk for postoperative complications, in which leakage has been associated with both decreased survival [2] and increased local cancer recurrence [9]. Interventions to reduce anastomotic complications after GI surgery would have a significant impact on improving overall postoperative patient outcomes.

Whereas the etiology of anastomotic breakdown is multifactorial, with contributing factors from both the patient and surgeon, the final common pathway frequently involves a combination of anastomotic tension, compromised tissue perfusion, and decreased oxygenation—factors shown to be key determinants of anastomotic viability [11–14]. These concepts were demonstrated in 1987 by Sheridan et al. [15] showing higher rates of colon anastomotic leakage in patients with decreased tissue oxygen tension. Subsequently, animal models have confirmed the importance of adequate blood flow and oxygenation for the creation of a sustainable anastomosis [11, 13]. Anegg et al. [16] demonstrated that decreased oxygen tension at the esophago-enteric anastomosis is associated with an increased leak rate in humans. Overall, these data suggest that intraoperative recognition of peri-anastomotic tissue oxygenation could help minimize postoperative anastomotic complications by guiding surgeons to perform maneuvers to increase tissue perfusion and/or fashion anastomoses at sites of optimal tissue healing.

Current standards of assessing viability at the anastomosis rely on clinical determinants, such as visual inspection of the resection margin and palpation of mesenteric arterial flow—notably subjective and crude parameters. Intraoperative Doppler techniques have been shown to improve anastomotic failure rates by confirming adequate blood flow to the pancreatic side of the pancreaticojejunostomy during pancreatic resection [17]. The utility of intraoperative Doppler, however, is limited by arteriovenous shunting, which causes nonnutritive flow and lack of oxygen delivery data [18]. Tissue tonometry, a frequently cited method for determining gastric mucosal oxygenation, in fact measures tissue pH and readouts are confounded by systemic processes that alter tissue CO₂, such as sepsis or CO₂ retention [19]. Furthermore, tonometry has demonstrated variable results and poor sensitivity in preclinical models of tissue ischemia [20]. Pulse oximetry, routinely used intraoperatively to measure peripheral blood oxygen saturation (SpO₂), uses optics to determine the changes in light absorption based on the volume of blood in the tissue and is thus dependent on the systemic blood circulation and does not necessarily reflect actual tissue oxygen tension. Furthermore, these devices are not technically amenable to

Table 1 Limitations of currently available intraoperative oximeter technologies for continuous monitoring of local tissue oxygenation

Oximeter design	Benefits	Limitations
Electrochemical sensor [22]	Noninvasive Moderate sensitivity	Requires vasodilation Poor accuracy
Reflectance electro-optical PPG probe [23]	Intraoperative Disposable sensor Accurate	2-min dark room calibration Motion artifact Large probe size
Intrapartum pulse oximeter [24, 25]	Noninvasive Signal processed away from sensor	Limited applicability Large probe Poor sensitivity Systemic, not local O ₂
Reflectance esophageal pulse oximeter [26]	Blood gas analysis and co-oximetry Reliable High signal-to-noise	Potential interference from acidic stomach/bowel

PPG Photoplethysmographic

placement on intra-abdominal or thoracic organs. Currently, pulse oximeters are not routinely available to measure local tissue oxygen saturation (StO₂) at the anastomotic site. Table 1 elucidates the current oximeter technologies available for clinical use and their limitations in applying to intraoperative monitoring.

Herein we describe the results of a novel intraoperative wireless pulse oximeter (WiPOX), which enables the surgeon to monitor tissue oxygenation in real-time at the anastomotic site, thereby maximizing the ability to create a successful, sustainable anastomosis by targeting well-perfused tissue.

Materials and methods

The wireless pulse oximeter (WiPOX) was designed and constructed through collaboration between the Division of Thoracic Surgery at Memorial Sloan-Kettering Cancer Center (MSKCC) and the Department of Bioengineering at the City College of New York (CCNY). The initial proof-of-principle prototype was constructed as a senior bioengineering project by a group of eight students with mentoring from senior authors (PSA, NR, and MB). The device was fabricated using materials already approved for use in humans in the operating room by the Food and Drug Administration (FDA). Reflectance oximetry technology was utilized to facilitate application to intra-abdominal organs in contrast to traditional transmission oximetry as is used in finger and earlobe oximeters, which requires

transmission through tissues—a technical limitation when attempting to assess solid organs and bowel (Fig. 1). Care was taken to ensure size parameters appropriate for use via laparoscopic and thoracoscopic 12-mm ports.

Preliminary human accuracy testing assessed the WiPOX device in healthy human volunteers. The WiPOX was evaluated against two commercially available pulse oximeters as gold standards: the Nonin Onyx® 9500 (Nonin Medical, Inc., MN) and the SPO 5500™ (SPO Medical, CA) finger oximeters. For each of ten trials, an average was taken for the two commercial oximeters. The percent differences between oxygen saturation for the WiPOX device and the average measurements from the commercial devices were recorded.

The WiPOX was next tested *in vivo* during animal operations using adult Sprague-Dawley rats (Charles River, MA) and adult female Yorkshire swine (Archer Farms Inc., MD). Procedures were approved and performed in accordance with the standards set forth by the Institutional Animal Care and Use Committee (IACUC). Rats were anesthetized using inhaled isoflurane anesthesia via nose cone. Swine were anesthetized with ketamine and xylazine, endotracheally intubated, and maintained on mechanical ventilation by veterinarians from the Veterinary Services Department at MSKCC. Following adequate anesthesia, midline laparotomy was performed in swine and the stomach and small bowel were mobilized. StO₂ measurements were taken using the WiPOX device from healthy stomach and small bowel and compared with systemic SpO₂. To demonstrate WiPOX ability to detect StO₂ variations in tissue hypoxia, experiments were performed

in rats. The stomach was mobilized and an anterior gastrostomy created by raising a flap of stomach wall, which remained attached by a narrow tissue connection to the lesser curvature, which we ensured had normal initial StO₂ (95–100%); we then induced ischemia by placing a clamp across the flap base (Fig. 2A, B). StO₂ was measured using the WiPOX device on both the serosal and mucosal surfaces of the healthy vascularized stomach and compared to the compromised tissue flap (Fig. 2C, D). To investigate whether WiPOX could be efficacious in detecting renal hypoxia, as in the case of warm ischemia during partial nephrectomy [21], the right kidney was mobilized and StO₂ measured from the kidney surface using the WiPOX before and after clamping of the vascular hilum. For both stomach and kidney experiments, measurements were performed in triplicate in each of three rats with means and standard errors reported. Animals were euthanized while under general anesthesia after all procedures.

Results

WiPOX design

Clinical prototype devices were constructed by the collaborative CCNY/MSKCC group to measure intraoperative StO₂. The design concept employs multiple photodetectors arranged around a single infrared/red LED. The probe contains the reflectance sensor housed in a cylindrical compartment designed to optimize functionality for both open and minimally invasive use and ergonomics. The

Fig. 1 Handheld WiPOX device (A) utilizes reflectance oximetry (B) to allow for intraoperative application to solid organs and bowel, in contrast to traditional transmission oximetry (C). B and C Reprinted with permission from Macmillan Publishers Ltd. Journal of Perinatology 24: 366–371; 2004

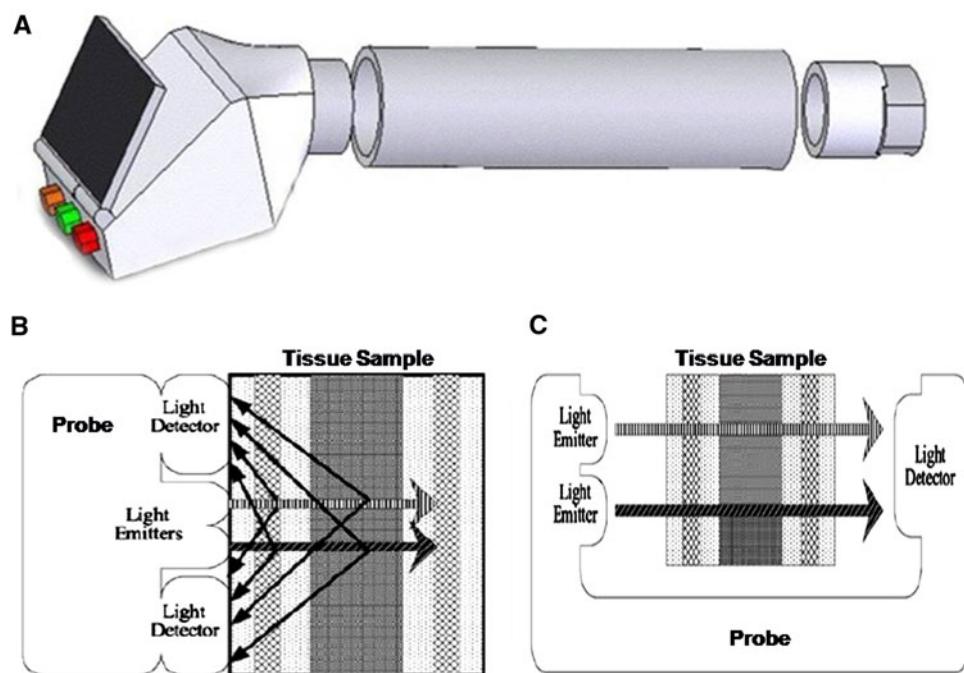
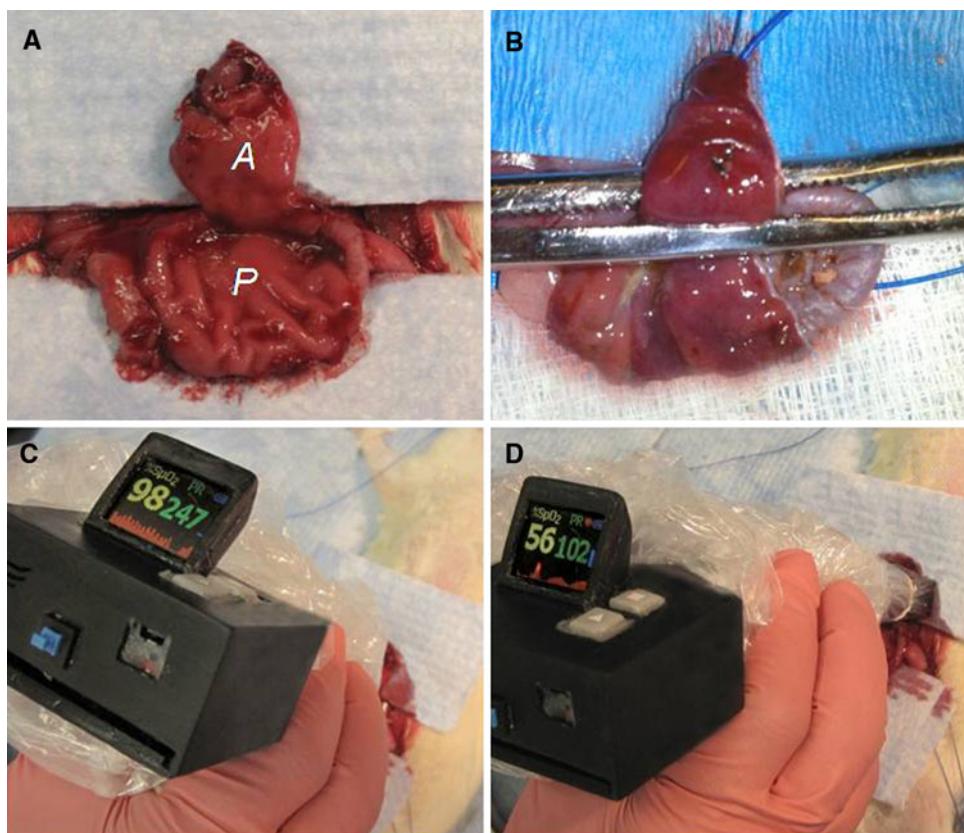


Fig. 2 WiPOX detected tissue hypoxia within 30 s of compromised perfusion demonstrated in the rat stomach. (A) Reflection of well-perfused anterior wall (*A*) from the posterior (*P*) stomach remaining connected at the lesser curvature. Transient reversible ischemia (B) created by clamping across the anterior wall base. StO₂ was measured on healthy (C) and compromised (D) stomach on both serosal and mucosal surfaces documenting detection of tissue hypoxia



sensor acquires StO₂ readings by direct contact with the tissue surface. The contact pressure-sensing head allowed for consistent, high-quality SpO₂ waveform readouts even in the presence of body fluids and blood. To prevent application pressure from compromising mucosal StO₂ measurements, a new generation device uses a spring-loaded

sensor to allow for optimal pressure application. Local oxygen saturation levels are determined by applying the device to any point on the gastrointestinal tissue surface. The onboard microcontroller and LED array permit noninvasive pulse oximetry using modified signal processing algorithms for real-time intraoperative application.

Table 2 WiPOX device intraoperative specifications

Specification	Optimal range	WiPOX
pH range	Gastric: 4.8 Intestinal: 7.1	Device functions at physiologic pH range 4.8–7.1
Temperature range	Physiologic organ temperature: 30–40°C Operating room temperature: 18–26°C	Device functions at physiologic temperature range Sensor/processor accurate at OR temperature range
Tissue contact area dimensions	Spatial resolution <30 mm	Device can detect tissue oxygenation differences within 30 mm distances
Sensor-tissue contact pressure	4–40 kPa	Device optimized to maintain sensitivity within pressure range safe for tissues
Sensor energy dissipation	<2 mW (commercial standard)	<1–5 µW energy dissipation Device does not cause thermal tissue injury

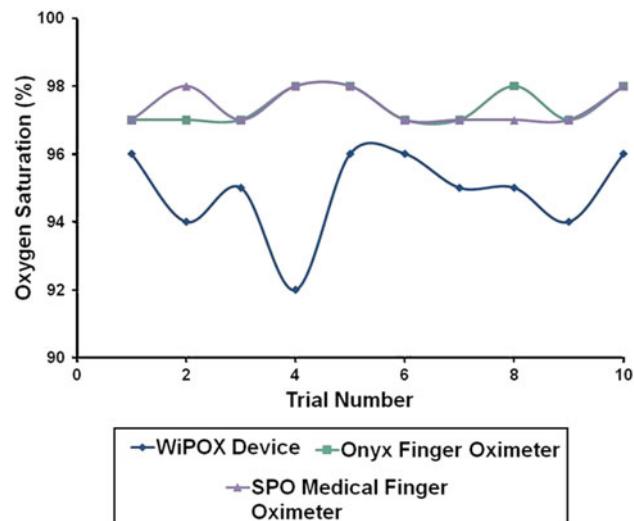


Fig. 3 WiPOX device demonstrated a high degree of accuracy compared with standard commercially available finger oximeters in healthy human volunteers. Final average relative accuracy over ten trials was 97%

Additionally, wireless technology was employed to create a wireless communication between the handheld device and the intraoperative monitors. The WiPOX device specifications meet the standards set forth by the FDA for device implementation in humans (Table 2).

Accuracy testing

Accuracy testing comparing WiPOX measurements in healthy human volunteers to standard commercially available pulse oximeters was obtained in ten independent trials. The final average relative accuracy compared with standard pulse oximeters across all trials was 97%. Due to the inherent $\pm 2\%$ deviation for each commercial oximeter, the total relative accuracy was adjusted to 95% (Fig. 3).

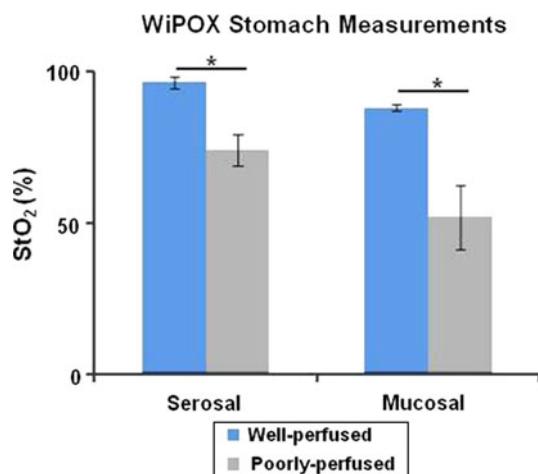


Fig. 4 WiPOX device detected tissue hypoxia in the rat stomach after compromised perfusion. The drop in StO₂ was greater in mucosal (52 vs. 88%) compared with serosal (74 vs. 96%) evaluations. WiPOX detected tissue hypoxia before visible signs of ischemia (* $p < 0.005$)

Fig. 5 WiPOX device detected kidney hypoxia in the rat after compromised perfusion. WiPOX revealed decreased StO₂ on the kidney surface after clamping of the vascular hilum (35 vs. 73%; * $p < 0.005$)



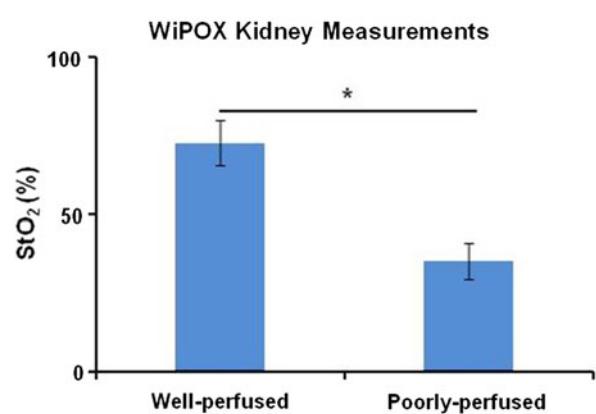
Preclinical trial

The WiPOX efficacy was evaluated intraoperatively during bowel surgery in rats and swine. Application of the WiPOX in swine demonstrated normal StO₂ and pulse rates in healthy small bowel and stomach compared with systemic SpO₂ values. Within 30 s of mesenteric vessel occlusion, the WiPOX device detected bowel hypoxia in the devascularized segments despite normal appearance of tissue on gross inspection (data not shown).

In rats, hypoxia was detected in the devascularized stomach compared with healthy stomach by applying the WiPOX device to the stomach serosa (74 vs. 96%, $p < 0.005$); this difference was magnified when mucosal measurements were obtained (52 vs. 88%, $p < 0.005$; Figs. 2, 4). Notably, the WiPOX detected serosal and mucosal hypoxia before visible signs detectable by the surgeons. These observations were reproduced in repeat experiments. In addition, after clamping of the hilum, kidney hypoxia was detected by the WiPOX compared with normal kidney ($p < 0.005$), which similarly occurred before overt signs of ischemia (Fig. 5).

Discussion

Anastomotic leakage continues to occur with a high frequency after gastrointestinal surgery and portends a poor overall patient outcome. Patients who experience anastomotic breakdown suffer prolonged hospitalization, decreased quality of life, increased mortality, and consequently increased healthcare costs. Attempts to reduce the rate of postoperative anastomotic leakage after esophagogastrectomy have been largely unsuccessful as illustrated by the essentially unchanged leak rates after esophagogastrectomy during the past two decades. However, evidence suggests that peri-anastomotic oxygenation contributes to



anastomotic healing [11, 15, 16, 22]; thus, there is compelling evidence that ensuring maximal tissue oxygenation will likely improve anastomotic viability. The WiPOX device represents a novel technology capable of real-time assessment of tissue oxygenation intraoperatively, thereby, aiding surgeons to select an optimal site for fashioning gastrointestinal anastomoses.

The WiPOX device is designed for use during open or minimally invasive procedures and integrates seamlessly with current intraoperative monitoring systems. Care has been taken to optimize the WiPOX device for application in various intraoperative conditions. In our observations during the course of the rat and pig experiments, we found that body fluids, such as blood, ascites, or bile, do not interfere with WiPOX efficacy; this is in contrast to other intraoperative oximeters in which these common intraoperative fluids have been reported to potentially decrease oximeter accuracy. In addition, light-emitting oximeters, such as the T-Stat® 303 Microvascular Tissue Oximeter (Spectros, Portola Valley, CA), are vulnerable to signal interference from the endoscopic light used during minimally invasive surgical procedures. These devices also are expensive; the T-Stat® oximeter base unit costs more than \$29,000 and nonreusable probes each cost \$350 [23].

The preclinical animal studies described in this report demonstrate the efficiency and accuracy of the WiPOX in measuring tissue oxygenation intraoperatively. More importantly, we have shown that the WiPOX is capable of detecting early tissue hypoxia at a point when no overt evidence of ischemia was observed by the surgeon. This is particularly important considering that tissue ischemia is a progressive process and subtle unrecognized tissue hypoxia could develop into significant tissue ischemia postoperatively. The data herein suggest that the use of WiPOX may detect otherwise occult peri-anastomotic ischemia and allow the surgeon to correct the anastomosis before completing the case. Similarly, in renal surgery, the use of WIPOX could help to minimize the occurrence of ischemia induced renal dysfunctional following partial nephrectomy [21]. These preclinical studies, however, are limited by the fact that the animals were not followed postoperatively to assess the association between WiPOX oxygenation data and rate of anastomotic leakage or tissue healing. These evaluations were not pursued because our goal was to expeditiously obtain “proof-of-principle” data for a timely application to begin a clinical trial using the WiPOX device in humans.

To validate the efficacy of the WiPOX in reducing anastomotic complications in humans, we have designed a prospective clinical trial for patients who undergo esophagogastrectomy for esophageal or GEJ cancer. The primary objective of this clinical trial is to determine whether introduction of the WiPOX to guide surgeon choice of

anastomotic site will decrease the postoperative anastomotic leak rate compared with historical controls.

Conclusions

The novel WiPOX device has demonstrated highly accurate and reproducible real-time assessment of tissue oxygenation in human volunteers as well as intraoperatively during gastrointestinal surgery in animals. Furthermore, the WiPOX reliably detected tissue hypoxia after bowel resection in rats and swine before overt clinical signs of ischemia. A clinical trial to investigate the efficacy of the WiPOX in human patients is underway. Routine intraoperative use of the WiPOX for the real-time detection of peri-anastomotic tissue oxygenation may help surgeons reduce anastomotic complications after gastrointestinal surgery. In addition, this device is easily applicable for use in other indications, such as intra- and postoperative monitoring of tissue oxygenation in microsurgery flaps.

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