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Review Article

Techniques for intraoperative evaluation of bowel viability in mesenteric ischemia: A review

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ABSTRACT

Acute mesenteric ischemia (AMI) is a deadly and common surgical emergency. While several imaging modalities aid in the diagnosis of AMI preoperatively, there are limited intraoperative tools for surgeon decision making regarding bowel viability. Here we offer a review of the utility and limitations of the many extensively studied techniques. We classify each of these modalities into three hallmarks of healthy bowel: oxygenation, myoelectric activity and perfusion. Finally, we offer a brief discussion of emerging and promising techniques to assist surgeons in intraoperative decision making for patients with mesenteric ischemia.

Introduction

Background

Acute mesenteric ischemia (AMI) accounts for approximately 1:1000 acute hospital admissions in the United States, and the incidence is on the rise likely due to an aging population as well as the prolonged survival of critically ill patients.[1] AMI can be caused by a reduction in blood flow from arterial occlusion, venous occlusion, arterial vasospasm, or a low-flow state. Regardless of the etiology of the disease, rapid diagnosis and treatment of AMI is of critical importance.[2]

Several imaging modalities are available to aid in the diagnosis of mesenteric ischemia preoperatively. A computed tomographic (CT) angiography is the gold standard initial imaging study for patients for whom there is a high index of suspicion.[3] Ideally, the CT is performed without oral contrast to avoid obscuring the mesenteric vasculature. CT scan findings concerning for acute mesenteric ischemia include bowel wall thickening, portal venous gas, and intestinal pneumatosis.

If left untreated, intestinal ischemia may lead to transmural necrosis of the bowel wall leading to an overwhelming inflammatory response and death. The initial management of AMI includes gastrointestinal decompression, fluid resuscitation, antibiotics, and in many cases, operative intervention. The goal of surgery is to assess the bowel, restore blood flow, and resect any areas of bowel that appear nonviable while leaving intact the bowel that will ultimately survive. The tools for diagnosing intestinal ischemia intraoperatively are limited, especially in circumstances in which the bowel appears to be “dusky” or threatened but not clearly ischemic. In this case, a temporary abdominal closure via a negative pressure wound therapy device is convenient in order to provide an opportunity for a second-look surgery. At this time, the bowel is often more clearly demarcated as viable or non-viable.

This article provides an overview of available techniques and tools for intraoperative assessment of bowel viability for AMI (Table 1). The goal of this review is to highlight the need for further research and investment in tools for intraoperative bowel assessment to improve patient outcomes in this population that experiences mortality rates as high as 60–80%.[4]

In addition to traditional surgical inspection of the bowel, available techniques of intraoperative assessment of bowel viability rely on three main characteristics of healthy bowel: oxygenation, myoelectric activity, and perfusion. The intraoperative absence of any one of these criteria is seen as a sufficient predictor of bowel nonviability and grounds for surgical resection when correlated with clinical judgement. This review is structured around these three hallmarks of healthy bowel and the intraoperative techniques

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Table 1
Literature on mesenteric ischemia grouped by techniques of intraoperative bowel assessment.

Pulse Oximetry/Photoplethysmography (PPG)	Locke et al., 1984
	Pearce et al., 1987
	DeNobile et al., 1990
	Dyess et al., 1991
	Alos et al., 1993
	Avino et al., 1995
	Tollefson et al., 1995
	La Hei and Shun, 2001
	Erikoglu et al., 2005
Electromyography (EMG)	Shah and Andersen 1981
	Brolin et al., 1986
	Brolin et al., 1987
	Brolin et al., 1989
	Orland et al., 1993
	Holmes et al., 1993
	Brolin et al., 1995
	Brolin et al., 1997
	Dutkiewicz et al., 1997
	Basdanis et al., 1999
	Ladipo et al., 2003
Doppler Ultrasound	Wright and Hobson, 1975
	Hobson et al., 1979
	O'Donnell and Hobson, 1980
	Cooperman et al., 1980
	Bulkley et al., 1981
	Shah and Andersen, 1981
	Mann et al., 1982
	Pearce et al., 1987
	Freeman et al., 1988
	Johansson, 1988
	Lynch et al., 1988
	Brolin et al., 1989
	Ovcharenko et al., 1989
	Johansson et al., 1989
	Alos et al., 1993
	Ballard et al., 1993
	Avino et al., 1995
	Redaelli et al., 1998
	Kaser et al., 2012
	Khripun et al., 2012
Fluorescein	Stolar and Randolph, 1978
	Bulkley et al., 1981
	Marfuggi and Greenspan, 1981
	Mann et al., 1982
	Amano et al., 1984
	Carter et al., 1984
	Marzella et al., 1984
	Pearce et al., 1987
	Freeman et al., 1988
	Lynch et al., 1988
	Whitehill et al., 1988
	Dyess et al., 1991
	Bergman et al., 1992
	Ballard et al., 1993
	Holmes et al., 1993
	Tollefson et al., 1995
	Horstmann et al., 2000
	McGinty et al., 2003
	Paral et al., 2007
Radiolabled Microspheres	Lanzafame et al., 1983
	MacDonald et al., 1993
Near-Infrared Imaging	Matsui et al., 2011
	Iinuma et al., 2013
	Diana et al., 2014a
	Diana et al., 2014b
	Nowak et al., 2015
	Alemanno et al., 2016
	Karampinis et al., 2018
	Liot et al., 2018
	Nakagawa et al., 2018
	Khitaryan et al., 2019

that leverage their presence or absence for surgical decision-making.

Standard clinical approach

Hands and eyes

Traditional inspection of the bowel has been shown to be sub-optimal for the accurate diagnosis of intestinal ischemia.[5] The extent and severity of intestinal ischemia is determined by noting the appearance of the abdominal contents (color, distention), peristalsis, arterial pulsations in the mesenteric arcades, and bleeding from cut surfaces. Using these traditional methods, if the bowel is noted to be dark in color (black or blue) in comparison to surrounding healthy bowel, it is presumed to be non-viable or ischemic and requires resection. Additionally, if the bowel is distended to the point where there is thinning of the bowel wall or even a perforation, that bowel is also considered non-viable. Many surgeons use their hands and eyes to look for the presence or absence of peristalsis or mesenteric pulsation to evaluate whether blood flow is adequate and will use only these methods to determine whether bowel should be resected or remain in place.

In cases in which the bowel is frankly necrotic, the decision to resect is obvious. However, in many instances, it is unclear at the initial operation whether the bowel is viable or nonviable. In these situations, the bowel is often described as "dusky" or "patchy." Especially when a significant portion of bowel has already been removed, the surgeon may be hesitant to resect additional bowel without a clear diagnosis of ischemia in order to avoid short gut syndrome and the complications that go along with it, including intestinal failure, undernutrition, and hydro-electrolytic abnormalities, which often require treatment with intravenous supplementation or long-term home parenteral nutrition.[6,7,8] In these circumstances, the surgeon will often employ damage control surgery. This involves a temporary abdominal closure and return to the intensive care unit for continued monitoring and resuscitation. In the ICU, attention is paid to the hemodynamics of the patient. If the patient declines without another source of sepsis, it is often inferred that the bowel has declared itself as dead. In those circumstances the patient is brought back to the operating room earlier for definitive resection.

In circumstances in which the patient remains stable or improved, the patient usually returns to the operating room within 24–48 h for a second look and hopeful abdominal closure.[9] The use of second look laparotomy is associated with a reduction in morbidity and mortality in selected patients.

Oxygenation

Pulse oximetry/photoplethysmography

To assess bowel viability, surgeons have taken advantage of the ubiquitous technology of photoplethysmography (PPG), seen most commonly in the operating room as a pulse oximeter. PPG traditionally measures oxygen saturation in arterial blood noninvasively using electromagnetic pulses in two wavelengths, usually in the red and infrared regions.[10] These signals take advantage of the detected pulse and the different absorption spectra of oxygenated and de-oxygenated hemoglobin so that transmittance of light through the tissue, usually a finger, can be measured and used to calculate oxygen saturation (SpO_2). With oxygenation as a hallmark of healthy tissue and a proxy for adequate arterial perfusion, pulsatile PPG and tissue surface oximetry have been used effectively to predict bowel viability intraoperatively in animal models of ischemia.[11,12,13,14] Indeed, one set of experiments in rabbits suggests

that intraoperative assessment of bowel SpO_2 measured via pulse oximetry is sensitive enough to differentiate between varying degrees of intestinal necrosis, ranging from mucosal necrosis to complete transmural necrosis.[15] The authors demonstrate 100% sensitivity with pulse oximetry and conclude that intraoperative assessment of bowel viability with pulse oximetry has predictive value and may be able to reduce the number of second-look operations. These animal models also suggest that bowel surface oximetry and PPG are not only effective, but compare favorably to other techniques of evaluating intestinal viability, including ultrasonography, standard clinical evaluation, and intravenous fluorescein.[161718]

Despite these positive results, the literature remains conflicted on the applicability of PPG and pulse oximetry in the intraoperative assessment of bowel viability. Firstly, there is no laparoscopic utility of this technology, so it requires an open operation. Additionally, from Avino et al., although the absence of a pulsatile PPG tracing and SpO_2 <90% were predictive of altered perfusion in their canine model of bowel ischemia, they were unable to distinguish between complete and partial ischemia using this method.[11] In other words, surface oximetry was only capable of measuring transmural necrosis and could not detect early mucosal necrosis. This distinction is of the highest value to surgeons seeking to maximally preserve healthy or recoverable bowel while resecting necrotic bowel to avoid the necessity and complications of a second-look operation. Additional studies in animal models suggest that PPG and pulse oximetry are either not effective, or compare poorly to other techniques including standard clinical criteria, fluorescein flowmetry, or Doppler ultrasonography (DUS).[19] Such conflicting, and now outdated results emphasize the need for further research on techniques of intraoperative bowel viability and the determination of a definitive best practice to augment surgical decision-making.

Myoelectric activity

Electromyography

Electromyography (EMG) takes advantage of the contractile abilities and threshold stimuli of non-ischemic bowel, using this characteristic of healthy bowel to assess for ischemia intraoperatively. A technique traditionally used to assess skeletal muscle contractility in neuromuscular diseases, EMG has also been investigated in animal models of AMI.[20212223] EMG was shown to be an effective predictor of bowel viability in canine models of AMI, suggesting the potential for clinical application.[2425] EMG is particularly useful in the context of assessing bowel viability because of its quantitative potential, leading investigators to study the threshold stimulus and the possibility of identifying a maximum stimulus threshold to guide surgical decision-making.[2627]

In comparison studies in animal models, EMG was shown to outperform clinical judgement alone, and its quantitative potential serves as a possible clinical advantage over DUS.[28] However, a separate study conducted by Holmes et al. suggests that EMG has limited predictive value.[29] Semmlow et al. citing a series of canine studies, suggest that early results show EMG's superiority to visual or flowmetric assessments, but that improvements in instrumentation and technique are needed before translation to use in clinical AMI.[5]

Clinical translation of EMG has been evaluated in elective surgery, where the frequency and amplitude of slow waves in ischemic bowel were shown to be markedly diminished when compared to healthy bowel, a distinction that also correlated with histological changes of mild, moderate, and severe bowel ischemia in a cohort of 16 patients.[30] Despite these preliminary successes, EMG has largely fallen out of favor in AMI, presumably due to the risks associated with electrodiagnostics in critically ill patients as well as the complexity of the technique.[3132]

Perfusion

Bowel viability can also be assessed intraoperatively based on measures of perfusion and flowmetry. The most common applications of this principle for assessing viability in mesenteric ischemia are ultrasonography and fluorescein flowmetry.

Doppler ultrasonography and laser Doppler flowmetry

DUS has been proposed as a viable intraoperative tool for bowel viability assessment since the latter part of the 20th century.[3334] Related techniques, including laser doppler flowmetry (LDF), have also been investigated and deemed sensitive and feasible for application in mesenteric ischemia.[35] LDF, which takes advantage of the Doppler effect of a laser beam rather than sound to assess perfusion, has quantitative potential, an improvement over DUS. In a randomized control study of 109 patients presenting with AMI, use of intraoperative LDF to assess bowel viability led to a significant decrease in postoperative complications and mortality compared to clinical judgement alone.[36] However, LDF remains a novelty compared to DUS due to its complexity and poor integrability into the surgical workflow. This rebuff to LDF in favor of qualitative DUS, despite promising clinical research, demonstrates the importance of ease of use and integrability when evaluating intraoperative tools.

DUS is a safe and non-invasive technique to measure blood flow using reflected sound waves and the Doppler effect, and is popular for its wide applicability and relatively low cost. These results are corroborated by a range of cohort studies and animal models concluding that DUS is an effective, feasible, and cost-efficient adjunct to standard clinical judgement.[3738394021] DUS has also been shown to maximize the preservation of viable bowel in multiple clinical experiences, one with $n = 23$ patients. DUS was proven to preserve viable bowel, avert postoperative complications, and avoid unnecessary second-look operations compared to clinical judgement alone.[4142]

These positive, clinical results have led to a number of comparison studies in animal models. These studies suggest that DUS is a better measure of intestinal viability in AMI compared to clinical judgement alone, and that DUS is comparable if not better than PPG and fluorescein flowmetry with the added benefit of cost-effectiveness and ease of use.[28434418]

However, similar to pulse oximetry and PPG, these positive results in the literature are tempered by publications highlighting the shortcomings and inefficacies of DUS for intraoperative assessment in AMI. The measurements are described as highly variable, and other studies question the accuracy and predictive value of the technology.[1145] And although LDF addresses some of the qualitative concerns associated with DUS, this related technique has its own shortcomings which preclude it from widespread, clinical adoption. The literature is also inconclusive in regards to the efficacy of DUS compared to PPG, fluorescein flowmetry, clinical judgement and histological comparison. For example, several additional studies show that DUS actually compares poorly to these methods in both clinical and animal models.[174647] Though the literature is inconclusive, DUS may have clinical applicability and efficacy in AMI, and its cost-effectiveness and ease of use make it a simple adjunct to standard, clinical intraoperative evaluation of bowel viability in AMI.

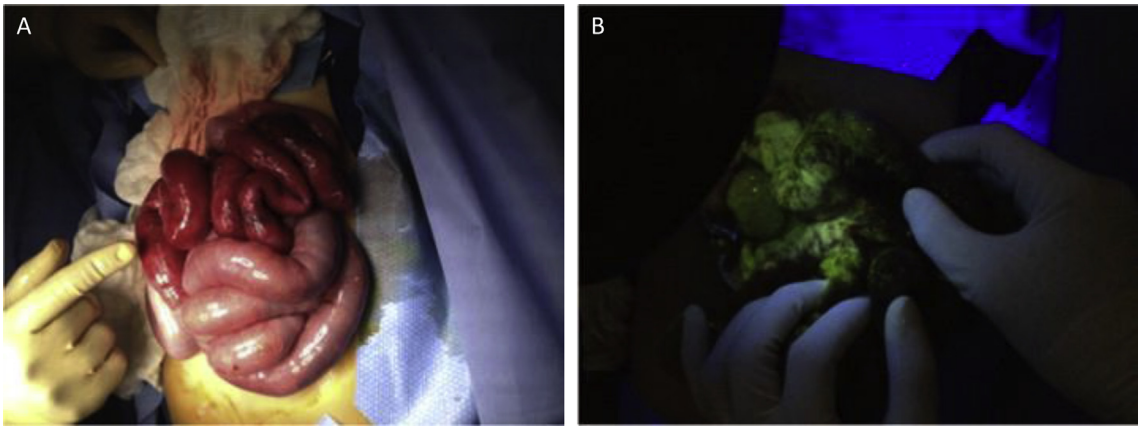

Fig. 1. A. Area of ischemic intestine, without evidence of necrosis with demarcation in the superior mesenteric vein territory. B. Wood's lamp after injection of IV fluorescence showing patchy perfusion to area of bowel in question. (Harris et al., 2014, published by Elsevier)

Fluorescein

Flowmetry with fluorescein dye is currently part of the accepted standard of clinical care for intraoperative assessment of bowel viability since Bulkley et al. published their seminal paper on intraoperative assessment of bowel viability.[4619] Sodium fluorescein, usually administered intravenously, is a fluorophore with excitation and emission peaks of 490 nm and 513 nm at physiological pH in 1% saline.[48] Fluorescein fluorescence can therefore be used to visualize perfusion in open laparotomies using a Woods Lamp or laparoscopically using an endoscope with the appropriate filters and UV excitation light. In preliminary animal models of AMI, perfusion assessment with fluorescein was shown to improve accuracy of surgical resection compared to standard clinical criteria.[495051] Additionally, clinical experience with selective use of fluorescein for intraoperative bowel viability assessment in patients at risk of developing ischemic colitis following aortic reconstruction also suggests reduced mortality in this patient population that has similar disease course to AMI.[52]

Comparison studies in animal models and clinical experience featuring fluorescein flowmetry have consistently demonstrated the superiority of dye-based perfusion monitoring for intraoperative bowel assessment as compared to standard clinical criteria, DUS, and pulse oximetry/PPG.[4746535445] However, these results are not universal, with some large animal models demonstrating no difference between fluorescein, DUS, and PPG, and an additional study showing that DUS actually outperforms fluorescein for intraoperative bowel assessment.[134318]

One major advantage of fluorescein flowmetry is its integrability into the operating room and its laparoscopic potential. Kam et al. demonstrated the feasibility of fluorescein-assisted laparoscopy in a canine model. Other groups confirmed fluorescein flowmetry as a valuable diagnostic procedure for early stage acute mesenteric ischemia as well as for second-look procedures in a porcine model (Fig. 1).[555657] Though the established treatment in the case of occlusive AMI remains open embolectomy, there remains a role for diagnostic laparoscopy in cases of uncertainty regarding the diagnosis or the extent of bowel necrosis, and in second-look operations.[1] Indeed, in this critically ill patient population, diagnostic laparoscopy may be equally effective in some hemodynamically stable patients as exploratory laparotomy while limiting additional mortality risk, length of stay, and complications.[5859] It is also possible that fluorescence guidance could prevent the conversion to laparotomy in some instances. With laparoscopic imaging, fluorescein flowmetry can be integrated into the modern operating room and can serve as a useful adjunct to clinical judgement in cases of AMI.

An important drawback of qualitative, intraoperative assessments of bowel viability in AMI is the low detection threshold of each technique, which is especially true for fluorescein flowmetry.[60] In AMI, though blood flow to the bowel is often limited, it is rarely completely absent. Whitehill et al. demonstrate this case in which qualitative assessments are at risk of leaving soon-to-be necrotic bowel *in situ* due to inadequate blood flow. Although perfusion following ischemic insult may be sufficient for distributing fluorescein throughout the tissue, it belies imminent tissue necrosis because the impaired perfusion fails to meet physiological needs. Additionally, as with many visible light fluorophores, fluorescein flowmetry is confounded by endogenous fluorophores and tissue autofluorescence that emit in the same wavelength, creating background noise and false signal. Shorter excitation and emission wavelengths also mean greater susceptibility to scatter and consequent limits to depth of signal penetration.[61]

To address the insufficiencies of qualitative flowmetry, a quantitative assessment of bowel viability using fluorescein fluorimetry was developed and shown to outperform both qualitative assessment and clinical judgement.[6229] However, the intraoperative utility of quantitative fluorescein fluorimetry in AMI is still in question. Any intraoperative tool is limited by the constraints and rhythms of the operating room. Quantitative fluorimetry is difficult to use, and therefore of limited value until further advancements are made.[44] Despite a lack of recent advancement, laparoscopic quantitative fluorimetry could prove to be a valuable avenue of continued research.[63]

Radiolabeled microspheres

The use of radiolabeled microspheres for perfusion assessment is a simple and effective technique for quantitatively measuring blood flow, and is mentioned here for its relevance in an experimental setting. It is regarded as a superior technique for quantitative potential as well as a lack of background signal.[6465] This technique, however, is not translatable to the clinic for bowel viability assessment in the setting of AMI due to the impracticality, cost, and unacceptable risks of radiation exposure inherent to the procedure.

Indocyanine Green

Indocyanine Green (ICG) is a near infrared (NIR) fluorophore

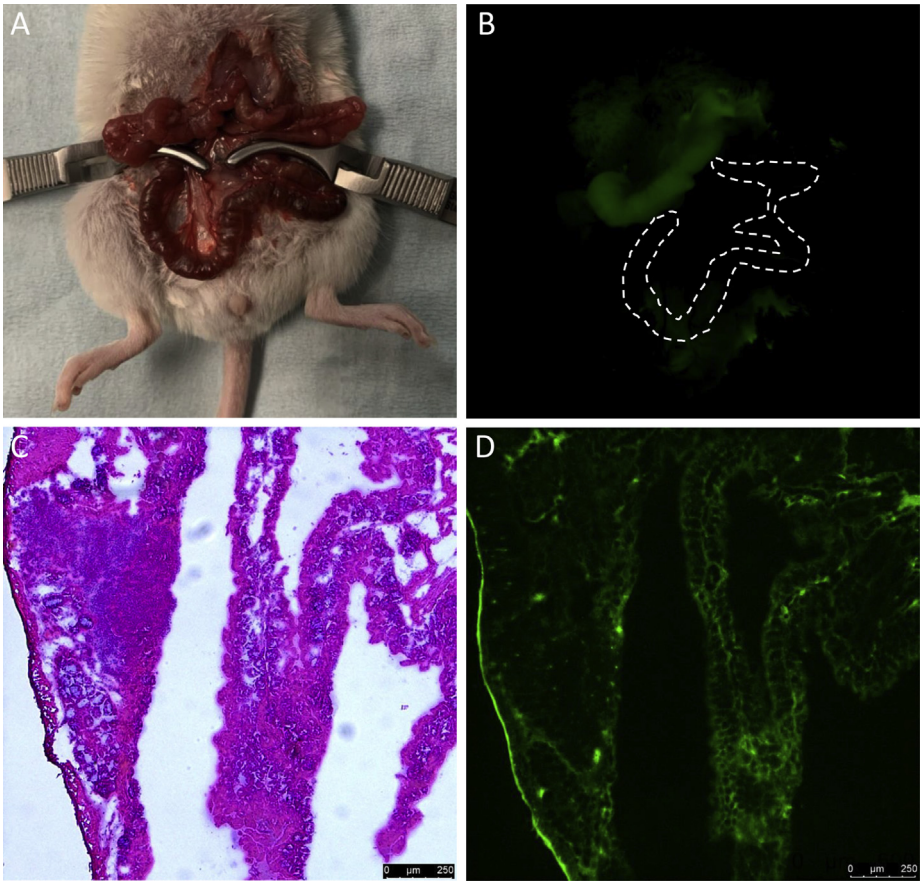

Fig. 2. Near-infrared imaging of mesenteric ischemia. A. Mouse model of mesenteric ischemia with clamps in place. B. NIR imaging of ischemic (white line) and viable bowel (green). C. H&E of viable bowel and D. Corresponding NIR fluorescence microscopy. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

with an emission peak of 832 nm in whole blood.[66] It has been used extensively in fluorescence angiography, in much the same way as fluorescein, but primarily in the elective surgical setting.[67] ICG utilization in the emergent setting, particularly in AMI, has not been well investigated to date, although early animal models and isolated case and cohort studies show promise. In porcine and murine models, ICG was shown to predict survival of ischemic bowel with greater accuracy than clinical judgement alone.[686970] Its efficacy was further demonstrated in individual case reports in the literature, where ICG detects ischemia not diagnosed on pre-op CT, may predict delayed intestinal ischemic complications, and confirms resection margins.[71727374] Sequential, single-center patient experiences of varying enrollment numbers also found that emergent intraoperative bowel viability assessment with ICG leads to a clinically significant alteration of the operation in 11–32% of cases, preserving bowel length and defining resection margins better than clinical judgement alone.[756776]

These recent positive results not only show renewed interest in intraoperative assessment of bowel viability for AMI, but also suggest the importance of revisiting the current standard of care, which holds fluorescein flowmetry as the first-line adjunctive tool for surgical decision-making. Theoretically, as a NIR fluorophore, ICG should outperform fluorescein when assessing bowel viability due to decreased background and greater tissue depth of penetration.[61] Additionally, with widespread commercial availability of the required open and laparoscopic imaging systems, intraoperative imaging with ICG is more readily available and easily integrated into the OR. Comparative studies, and ultimately a prospective trial, are warranted to re-evaluate intraoperative assessment techniques for bowel viability in AMI based on metrics that account for efficacy and clinical utility.

Our lab has developed a murine model of mesenteric ischemia and utilized NIR imaging and ICG in order to study bowel viability in an animal model. In our study, mice underwent laparotomy and occlusion of the distal branches of the superior mesenteric artery (SMA) using small vessel clamps. Following 60 min of occlusion time, the clamps were removed immediately prior to tail vain injection with 0.025 mg of ICG. Next, bowel was observed first using white-light followed by NIR imaging. NIR fluorescence (both macroscopically and microscopically) consistently and accurately predicted areas of bowel viability (Fig. 2). Viable fluorescent bowel was confirmed with H&E and fluorescence microscopy. Likewise, the lack of fluorescence using NIR imaging was indicative of ischemic bowel as confirmed with H&E. This study provides the groundwork for an ongoing translational research project using NIR fluorescence for predicting bowel viability in emergency surgery. It is noteworthy that while this technique is promising, it has many limitations. Following intravenous ICG administration, the dye will wash out from the tissue yet will likely be present in the bowel for up to hours afterwards. For this reason, the bowel can only be imaged accurately for perfusion once during surgery. Additionally, like many other perfusion methods, intravenous ICG will likely be more applicable to AMI caused by either arterial embolus, thrombosis, or a low-flow state, and will be of limited use for AMI

secondary to venous disease.

Discussion

The need for adjunct intraoperative techniques for the assessment of bowel viability in acute mesenteric ischemia is clear. Tissue oxygenation, myoelectrical activity, and perfusion are hallmarks of healthy bowel that show promise as avenues for intraoperative diagnostics in AMI. Currently, flowmetry with Doppler ultrasonography and fluorescein dye are the preferred methods employed in the operating room, with fluorescein flowmetry viewed as the gold standard due to efficacy and ease of use. The potential for combining modalities for intraoperative bowel assessment has been shown, and remains an avenue for further study.[77]

However, the evidence base for the current practice is both outdated and inconclusive, suggesting a need for further investigation to identify a best practice for surgical decision-making in AMI. As modern operating equipment adapts to integrate NIR imaging for perfusion angiography with ICG into commercial imaging platforms, our group sees an opportunity to reevaluate the standard of care in a translational study, based on early successes and a proven predictive value of ICG flowmetry for bowel viability assessment in a murine model of AMI. Intraoperative imaging and adjunctive assessment of bowel viability beyond reliance on clinical judgement is key to improving surgical outcomes in this patient population.

Declaration of competing interest

None of the authors listed have any disclosures or conflicts of interests to report.

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