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Received June 6, 2006. Accepted August 7, 2006.

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Diagnosis of chronic mesenteric ischemia by visible light spectroscopy during endoscopy

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Background: Chronic mesenteric ischemia can be difficult to diagnose by means of currently available clinical techniques. We developed a novel endoscopic device for objective measurement of GI mucosal ischemia.

Objective: Our purpose was to evaluate the performance of the device in patients with chronic mesenteric ischemia.

Design: A fiberoptic catheter-based visible light spectroscopy oximeter (T-Stat 303 Microvascular Oximeter, Spectros, Portola Valley, Calif) was used to evaluate 30 healthy control subjects and 3 patients with chronic mesenteric ischemia before and after successful percutaneous stenting.

Setting: Veterans Affairs Palo Alto Health Care System hospital.

Results: Normal mucosal (capillary) hemoglobin oxygen saturation was 60% to 73% in the duodenum and jejunum. In the 3 patients with chronic mesenteric ischemia, ischemic areas in the duodenum or proximal jejunum were found with mucosal saturations of 16% to 30%. After successful angioplasty and stent placement of the celiac, superior mesenteric, or inferior mesenteric arteries, the mucosal saturation in these areas increased to 51% to 60%.

Conclusions: This preliminary study suggests that chronic mesenteric ischemia is detectable during endoscopy by use of visible light spectroscopy and that successful endovascular treatment results in near normalization of mucosal oxygen saturation.

In current practice, timely diagnosis of acute and chronic mesenteric ischemia is often a challenge for clinicians. Classically, patients with acute mesenteric ischemia have profound abdominal pain and a paucity of physical

examination findings, whereas those with chronic mesenteric ischemia have severe postprandial abdominal pain and a fear of eating.¹⁻⁵ However, many patients do not have typical clinical presentations, and other conditions can also cause abdominal pain suggestive of ischemia. Patients with chronic ischemia can deteriorate as their vascular disease progresses and leads to bowel infarction. Definitive diagnosis of mesenteric ischemia can be difficult

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0016-5107/\$32.00
doi:10.1016/j.gie.2006.05.007

before progression to bowel infarction. Furthermore, angiography of the mesenteric vessels, which is considered the reference standard for diagnosis, provides detailed anatomic data rather than a physiologic assessment of the adequacy of intestinal blood flow. Stenotic or occlusive lesions of the superior mesenteric artery and other major vessels can be found in asymptomatic patients in whom collateral flow has compensated successfully.¹ Traditionally, the diagnosis of chronic mesenteric ischemia therefore requires a compatible history and significant angiographic lesions in at least 2 of the 3 major arteries supplying the gut: the celiac, superior mesenteric, and inferior mesenteric arteries. Remarkably, there are patients who have adequate collaterals from other vessels and who have no signs or symptoms of ischemia despite severe atherosclerotic disease of all 3 arteries.¹

Substantial progress has been made in noninvasive radiologic techniques in the past 2 decades, and several options now exist for evaluating the mesenteric arteries noninvasively. Duplex US is used to measure peak systolic velocity in the celiac and superior mesenteric arteries; high velocities are indicative of significant stenoses.⁶ CT angiography and magnetic resonance (MR) angiography now provide excellent images of the mesenteric vessels and are increasingly used clinically.⁷⁻⁹ However, from a clinical standpoint, an endoscopic method for detection of chronic mesenteric ischemia would be useful because there are many other conditions that present with abdominal pain or weight loss, and endoscopy is typically performed early in the workup of these patients.¹⁰ In this study, we describe our experience with a new visible light spectroscopy device that measures mucosal capillary hemoglobin oxygen saturation, a direct measure of the adequacy of mucosal perfusion.

Visible light spectroscopy, also known as reflectance spectrophotometry, is a technique that has been used endoscopically in a research setting to measure mucosal perfusion in the GI tract for more than 2 decades.¹¹⁻¹⁶ The technique uses white light delivered by a fiberoptic probe to directly measure the percent saturation of hemoglobin in the mucosa, relying on the marked difference in the absorption spectra of oxygenated and deoxygenated hemoglobin. Because most of the hemoglobin in the sampled region is located in mucosal capillaries, the measured saturation is a direct assessment of mucosal perfusion, and events that decrease oxygen delivery to below that required by the tissue will result in a decrease in the mucosal hemoglobin oxygen saturation. Early devices, available as far back as 1979, were limited by the ability to perform spectroscopy at only 3 wavelengths and the inability to perform sophisticated computerized analysis to eliminate the effects of scattering. As a consequence, studies addressing mucosal perfusion in various disease states tended to rely on pooled averages of multiple patients, and the technique was not very applicable as a clinical tool in individual patients. Modern instruments are capa-

Capsule Summary

What is already known on this topic

- A definitive diagnosis of mesenteric ischemia can be difficult before progression to bowel infarction.
- Suboptimal tissue delivery of oxygen results in a decrease in the mucosal hemoglobin oxygen saturation, which in turn can be measured by visible light spectroscopy.

What this study adds to our knowledge

- In 3 patients with symptomatic chronic mesenteric ischemia, disease was readily demonstrated by use of fiberoptic catheter-based visible light spectroscopy oximetry; successful percutaneous stenting led to a dramatic increase in the mucosal oxygen saturation.

ble of performing simultaneous measurements in hundreds of wavelengths with real-time signal processing to eliminate artifacts such as those from scattering. It is now possible to perform measurements continuously with a device that displays the tissue oxygen saturation continuously on a screen. Currently, the technique is limited to point measurements rather than being able to assess the entire endoscopic field simultaneously for focal areas of ischemia. In a previous study, our group demonstrated that measurements with the instrument used in this study yielded a bell-shaped curve between 60% and 80% in the colons of normal volunteers and that manipulations such as submucosal epinephrine injection and endoloop strangulation of polyp stalks resulted in rapid decreases to 18% to 36%.¹⁵ In this study, we describe our experience with the visible light oximeter in 4 patients with chronic mesenteric ischemia.

MATERIAL AND METHODS

The institutional review board at Stanford University and the Palo Alto Veterans Administration Health Care System approved this study. Informed consent was obtained from patients with suspected ischemia and from healthy control subjects for participation in the study. During upper endoscopy, enteroscopy, or colonoscopy, an endoscopic visible light spectroscopy oximetry probe (T-Stat 303, Spectros, Portola Valley, Calif) was passed through the accessory channel of the endoscope after meticulous irrigation of the target area to remove any bilious or fecal remnants. The probe was positioned approximately 1 to 5 mm above the mucosa. The endoscope light was briefly turned off, and a measurement of the tissue hemoglobin oxygen saturation was made. The device has a screen that displays the saturation in real time. The device automatically averages the signal for 0.25 second and displays

TABLE 1. Oximetry measurements of normal mucosa

Site	Patients	Measurements	Average (%)	SD (%)	Range	5th-95th percentile
Esophagus	30	99	71	5	62-83	63-79
Stomach	30	100	72	4	63-80	65-77
Duodenum/jejunum	25	125	66	5	56-80	60-73
Colon/rectum	25	248	73	5	61-86	65-81

the result after determining that the signal is stable, to avoid motion artifacts. The commercial instrument used in this study was an automated version of the device used in our previous studies.¹⁵ The only significant change from the instrument used in our prior reports is that the mucosal saturation is now displayed continuously in real time on the instrument's display. The patients in this study, including all controls, were all evaluated with the new device; none of the patients were reported in previous publications. In healthy patients, individual measurements were recorded. In ischemic patients, measurements were repeated at least twice and the results averaged. For calculation of interobserver correlation, tandem measurements of the same area were performed by one endoscopist with extensive experience with the technique (>200 cases) and compared with measurements performed by 1 of 4 endoscopists with limited experience (<10 cases).

Case histories of patients with chronic mesenteric ischemia

Patient 1 was a 66-year-old woman with a history of peripheral vascular disease, emphysema, and alcohol dependence who was admitted to the hospital because of 3 weeks of nausea, diarrhea, and severe abdominal pain exacerbated by meals. She lost 5 kg of weight during this period. On the morning of admission, she had 4 episodes of bloody diarrhea, prompting her to seek urgent care. On admission, she was cachectic and had stable vital signs. Her abdomen was nontender. Her hematocrit was 41% (normal 35%-45%). Her bloody diarrhea resolved spontaneously overnight. No discrete lesions were seen on upper endoscopy the following day, but the endoscopist noted that the mucosa of the fourth portion of the duodenum and proximal jejunum appeared slightly cyanotic; the mucosa in this area appeared slightly more purple than the typical pink of normal mucosa. On colonoscopy, there were patchy areas of erythematous, friable mucosa and multiple superficial erosions from the cecum to the sigmoid colon; the rectum was normal. This was thought to be consistent with ischemic colitis. An angiogram demonstrated severe stenoses of the celiac and superior mesenteric arteries and a prior aortobifemoral graft and absence of the inferior mesenteric artery (presumably from the previous vascular surgery). Celiac and superior

mesenteric artery stenting was performed. One month later, the patient was seen for follow-up. Her abdominal pain, nausea, and diarrhea had resolved completely. Her appetite was normal. Colonoscopy revealed complete resolution of the colonic lesions, and upper endoscopy to the proximal jejunum had normal results.

Patient 2 was a 60-year-old man with a history of diabetes mellitus and congestive heart failure, who was admitted for severe epigastric pain that started 24 hours before admission. He had had a similar pain 6 months previously that resolved spontaneously. Between the 2 episodes, he had mild abdominal pain exacerbated by meals. His weight decreased 10 kg during this time. Upper endoscopy with enteroscopy demonstrated superficial ulcers in the gastric fundus and antrum. There was a 12-mm superficial erosion in the distal second portion of the duodenum, and multiple diminutive erosions were found in the proximal jejunum. On angiography, he had complete occlusion of the superior mesenteric and celiac arteries and a 90% stenosis at the origin of the inferior mesenteric artery. The superior mesenteric artery was recanalized, angioplasty was performed, and a stent was placed percutaneously. After stenting, his abdominal pain resolved. His stools, which had been melanic since 1 day before admission, became grossly bloody for 24 hours after stenting. Repeat endoscopy and enteroscopy 48 hours after stenting demonstrated granulation tissue surrounding the superficial gastric ulcers and interval healing of the duodenal and jejunal erosions. On colonoscopy there were multiple superficial ulcers with erythematous borders in the cecum and ascending colon. The patient was seen in follow-up 4 months later, where he reported no further abdominal pain and his weight had increased by 10 kg.

Patient 3 was a 58-year-old man with diabetes mellitus and coronary artery disease who was seen for 8 months of epigastric pain that occurred 30 minutes after eating. He lost 15 kg during this period. In the last month before his presentation, the pain became significantly more severe. On endoscopy, there were scattered irregularly shaped superficial ulcers in the gastric body and a mottled cyanotic appearance. The mucosa in the duodenum and jejunum appeared slightly dusky. An angiogram demonstrated complete occlusion of the celiac artery, 95%

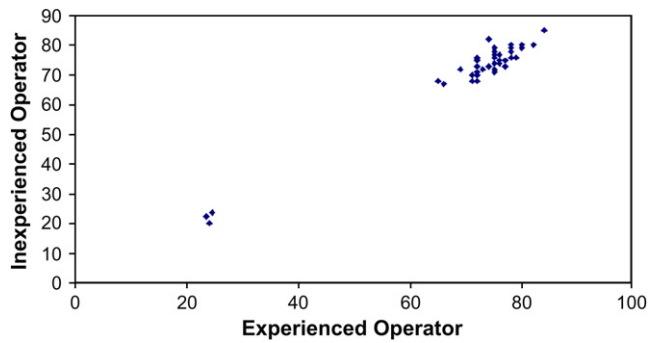


Figure 1. Scatter plot of tandem measurements performed by experienced operator and inexperienced operator.

stenosis of the superior mesenteric artery, and 99% stenosis of the inferior mesenteric artery. Angioplasty and stenting of the superior mesenteric and inferior mesenteric arteries was performed. The patient’s abdominal pain resolved immediately after the procedure. Endoscopy was repeated 3 days after the procedure, demonstrating normal mucosa in the stomach and small bowel, with complete resolution of the superficial gastric ulcers.

RESULTS

Measurements of normal mucosa in patients without a history of GI ischemia are summarized in Table 1. Normal mucosa had an average saturation ± SD of 73% ± 5% in the colon and rectum, 66% ± 5% in the duodenum and proximal jejunum, 72% ± 4% in the stomach, and 71% ± 5% in the esophagus. These normal values are based on 99 to 248 individual measurements in 25 to 30 patients in each region. In the duodenum and jejunum, the range was 56% to 80% and the 5th to 95th percentile of measurements was 60% to 73%.

Interobserver correlation was assessed in 8 patients by comparing a total of 46 paired measurements obtained by an endoscopist experienced with oximetry (>200 cases) with 1 of 4 endoscopists with limited experience (<10 cases). The results are shown in Figure 1. The correlation coefficient was 0.98. The average absolute difference in measurements was 2%.

The oximetry measurements are shown in Table 2. There was a statistically significant difference in tissue saturation in the duodenum/jejunum between the healthy patients and the 3 cases before intervention (*P* = .003 by 2-tailed *t* test with unequal variances). In patient 1, tissue oxygen saturation in the proximal jejunum increased from 30% before stenting to 60% after stenting. Endoscopic views of the proximal jejunum before and after stenting are shown in Figure 2. Smaller increases were observed in the duodenum and terminal ileum. In patient 2, tissue oxygen saturation in the distal second portion of the duodenum increased from 19% before stenting to

TABLE 2. Mucosal oximetry measurements in 3 patients with chronic mesenteric ischemia before and after successful percutaneous stenting

	Location	Prestenting	Poststenting
Patient 1	Gastric antrum	72	72
	Duodenum (second portion)	50	64
	Proximal jejunum	30	60
	Terminal ileum	58	72
	Cecum/ascending colon	63	77
	Transverse colon	74	67
	Rectum	65	66
Patient 2	Esophagus	73	69
	Gastric body	55	67
	Gastric antrum	57	75
	Duodenum (distal second portion)	19	51
	Proximal jejunum	42	56
	Cecum	76	
	Rectum	66	
Patient 3	Gastric body	74	69
	Gastric antrum	68	72
	Duodenal bulb	59	57
	Duodenum (second portion)	45	55
	Proximal jejunum	16	59

51% after stenting. In the proximal jejunum, there was an increase from 42% to 56%. Smaller increases were observed in the gastric body and antrum. The saturation in the esophagus was normal. In patient 3, proximal jejunal saturation increased from 16% to 59% with stenting, and midduodenal saturation increased from 45% to 55%. Interestingly, despite the superficial gastric ulcers and mottled gastric appearance, gastric saturation was normal before and after stenting.

DISCUSSION

The diagnosis of chronic mesenteric ischemia requires a compatible clinical history and angiographic demonstration of significant lesions in at least 2 of the 3 major mesenteric vessels.^{1,5} Although there has been significant progress in noninvasive imaging techniques with CT and MR imaging, a physiologic technique that evaluates the

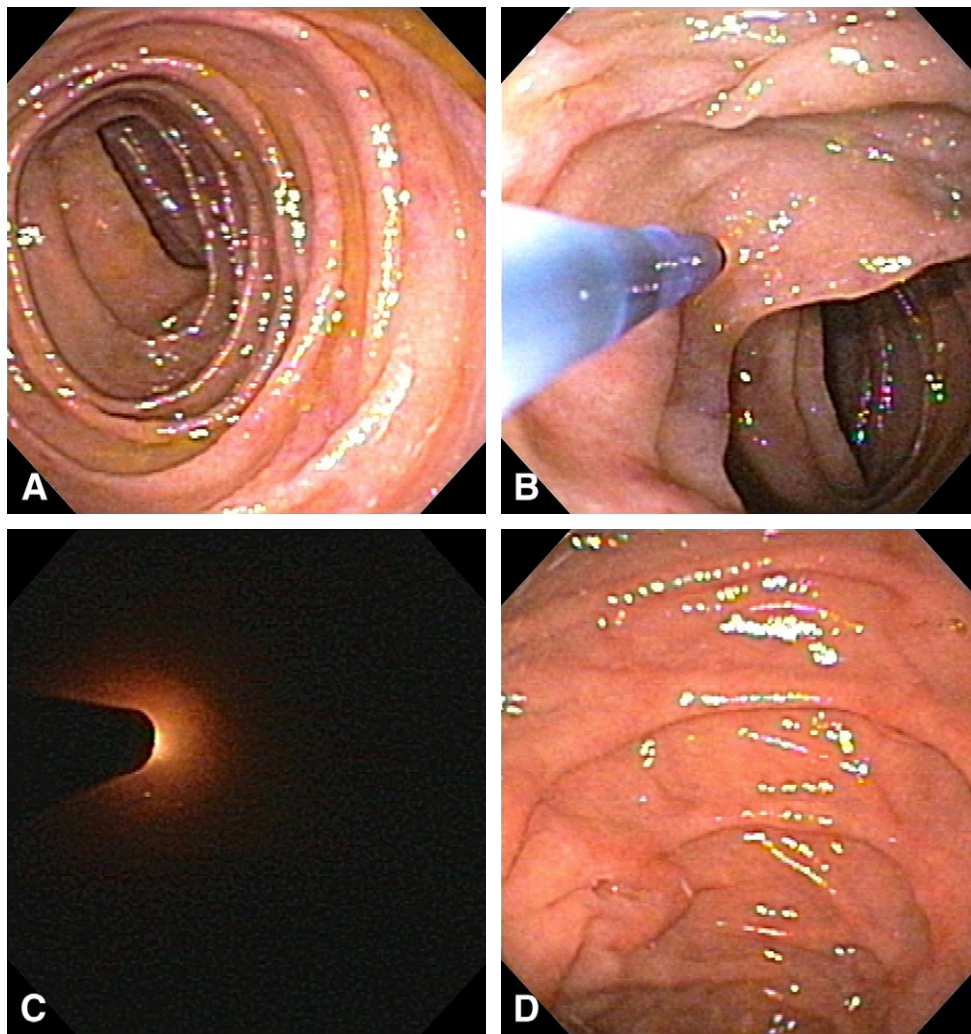


Figure 2. Endoscopic views of the proximal jejunum in patient 1. **A**, Appearance of mucosa before stenting, demonstrating slightly dusky mucosa. **B**, Oximetry probe has been positioned near mucosa for measurement. **C**, Endoscope light has been turned off during measurement. **D**, Normal appearance of mucosa 1 month after stenting of celiac and superior mesenteric arteries.

intestinal mucosa directly for ischemia would be valuable because some patients with chronic vascular disease are able to compensate for occlusion of major vessels by collateral vessels.¹ Previous research studies have suggested a possible role for tonometry, laser Doppler, MR oximetry, and MR measurement of mesenteric venous blood flow in the assessment of intestinal ischemia.^{8,11-14,17-19} However, these techniques have not been subjected to rigorous clinical evaluation and have remained limited to the research setting. In this study, we report on the application of visible light spectroscopy in 3 patients with chronic mesenteric ischemia. The device used in this study is available commercially (the cost is approximately \$20,000 for the device and \$1,000 for single-use oximetry catheters) and has received approval by the U.S. Food and Drug Administration for detection of ischemia.

Visible light spectroscopy exploits the difference in the absorption spectra of oxygenated and deoxygenated

hemoglobin to measure the average tissue hemoglobin oxygen saturation.¹¹⁻¹⁵ A fiberoptic probe, positioned adjacent to the mucosa during endoscopy, is used to illuminate the tissue with calibrated white light. A separate optical fiber within the probe collects light reflected from the mucosa for measurement by a spectrophotometer and subsequent computer analysis. The measured spectrum is decomposed into oxygenated hemoglobin, deoxygenated hemoglobin, and other components by a computer-fitting algorithm. The ratio of oxygenated hemoglobin to total hemoglobin (oxygenated plus deoxygenated) is the tissue hemoglobin oxygen saturation. Because most of the mucosal blood is in capillaries, with smaller amounts in arterioles and venules, this measurement corresponds closely to capillary hemoglobin oxygen saturation.¹¹ Multiple animal and human models of ischemia have demonstrated that normal tissue oxygen saturation is approximately 60% to 80% throughout the GI tract and that the

saturation decreases to 15% to 40% during experimental manipulations such as clamping of the vascular supply to the gut or submucosal epinephrine injection.^{11,15,16} In this study, the average mucosal saturation in healthy patients ranged from 66% \pm 5% in the proximal small bowel to 73% \pm 5% in the large intestine, in agreement with previous results. There was excellent interobserver correlation, with a correlation coefficient of 0.98, when paired measurements were performed by an experienced operator and an inexperienced operator. The measurement process is therefore highly reproducible and requires little technical skill.

The 3 patients described in this study had symptomatic chronic mesenteric ischemia that was treated successfully by percutaneous stenting, which is a relatively new but well-accepted treatment.²⁰⁻²³ In patient 1, oximetry demonstrated significant ischemia in the jejunum, with a tissue saturation of 30%. This increased to 60% after stenting of her celiac and superior mesenteric arteries. Less-dramatic increases were observed in the duodenum and terminal ileum. The tissue oxygenation measurements before and after stenting are therefore in agreement with the clinical improvement and the technical success of the procedure. Patient 2 had significant ischemia in the duodenum (19%) and jejunum (42%). After his superior mesenteric artery was stented, the saturation increased to 51% in the duodenum and 56% in the jejunum. The clinical improvement of the patient suggests that this amount of improvement in oxygenation was sufficient for symptom resolution. Interestingly, patient 2 also had mild ischemia in the gastric body (55%) and antrum (57%), which resolved with stenting of the superior mesenteric artery. The celiac artery, which typically supplies most of the gastric circulation, was occluded but was not stented during his procedure. We therefore ascribe the normalization of his gastric oxygenation to improved collateral supply after stenting of the superior mesenteric artery. This is consistent with the clinical perception that gastric ischemia is rare because of a relatively rich collateral circulation to the stomach. In patient 3, ischemia was readily demonstrated in the small bowel, with a jejunal saturation of 16% before stenting and a dramatic increase to 59% after stenting. In addition, he had multiple superficial gastric body ulcers that resolved 3 days after stenting of his celiac and superior mesenteric arteries, suggesting that they were also ischemic in origin. His gastric oximetry readings, however, were normal. It is therefore possible that he had intermittent gastric hypoxemia that was not evident at the time of endoscopy, as could perhaps occur with increased oxygen demand with meals. The mottled endoscopic appearance of the mucosa was considered by the endoscopist to be suggestive of continuing ischemia, but the measured tissue saturation was normal. There are several potential limitations with endoscopic appearance. It is subjective. In addition, there is generally no uniform calibration of endoscopy monitors and different endoscope models, so it is difficult

to compare mucosal color from different procedures. A further problem is that the color seen on endoscopy is affected by deeper structures and is therefore not necessarily indicative of the mucosal perfusion: an example of this is the purple hue seen during colonoscopy in areas of the colon adjacent to the spleen and liver. It would be interesting to formally evaluate the accuracy of visual endoscopic interpretation compared with oximetry, but this is beyond the scope of this study.

Our results suggest a possible role for visible light spectroscopy in the diagnosis of chronic mesenteric ischemia. In the 3 patients in this report, symptomatic ischemia was readily demonstrated on oximetry, and successful percutaneous stenting was followed by dramatic increases in the mucosal oxygen saturation. Possible limitations of this technique include the possibility that ischemia is patchy and could be missed, the possibility of ischemia in areas of the small bowel that are difficult to reach endoscopically, and the possibility that ischemia occurs only in response to increased metabolic demand, such as after a meal. The 3 patients presented in this article had relatively dramatic and progressive symptoms and substantially decreased mucosal oxygenation. We suspect that patients with milder symptoms, earlier in the course of the disease, will have oximetry values closer to normal. It will therefore be important to establish appropriate guidelines to assist clinicians in interpretation of mildly decreased values that can help predict which patients would benefit from intervention. Larger studies are clearly needed to evaluate the sensitivity and specificity of the technique and to develop rigorous protocols that define which areas of bowel to sample and whether to include provocative maneuvers such as feeding. The major limitation of our study is that it includes only 3 patients. The dramatic changes in capillary hemoglobin oxygen saturation seen in the 3 patients in this report, however, suggest that severe cases of chronic mesenteric ischemia are readily detected with this device. Other potential settings for the application of visible light spectroscopy include acute mesenteric ischemia and ischemic colitis. A hand-held version of the device is available for use during operative procedures to assist surgeons in determining whether the bowel is ischemic, and future studies will examine the utility of the instrument. In addition, the potential role of intestinal ischemia in other conditions, such as breakdown of surgical anastomoses and development of postoperative strictures, is currently being investigated.

DISCLOSURE

D. B. is employed by Spectros Corporation, which produces a commercial device for diagnosis of ischemia. S. F. serves on the scientific advisory board of Spectros corporation. D. B. and S. F. received equity in Spectros Corporation for their work in developing the device used in the

study. The device used in the study was provided free of charge by Spectros Corporation.

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Received February 13, 2006. Accepted May 10, 2006.

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