Decreased Conduit Perfusion Measured by Spectroscopy Is Associated With Anastomotic Complications

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Background. Gastric conduit ischemia during esophagectomy likely contributes to high anastomotic complication rates, yet we lack a reliable method to assess gastric conduit perfusion. We hypothesize that optical fiber spectroscopy (OFS) can reliably assess conduit perfusion and that the degree of intraoperative gastric ischemia is associated with subsequent anastomotic complications.

Methods. During esophagectomy, OFS was used to measure oxygen saturation (Sao_2) and blood volume fraction (BVF) in the distal gastric conduit at baseline and after gastric devascularization, conduit formation, and transposition. The Sao_2 and BVF readings were correlated to clinical outcomes.

Results. The OFS measurements were obtained in 23 patients during esophagectomy, four of whom previously underwent gastric ischemic conditioning. Eight patients developed anastomotic complications. Compared with baseline, conduit creation produced a 29.4% reduction in Sao_2 ($p < 0.01$), while BVF increased by 28% ($p = 0.06$). Patients with subsequent anastomotic complications demonstrated a 52.5% decrease in Sao_2 upon conduit creation compared with 15.1% in patients without complications ($p = 0.01$). Patients who underwent ischemic conditioning did not develop significant changes in Sao_2 ($p = 0.72$) or BVF ($p = 0.5$) upon gastric conduit creation.

Conclusions. Intraoperative OFS demonstrates significant alterations in gastric conduit oxygenation during esophageal replacement, which may be tempered by gastric ischemic conditioning. The degree of intraoperative gastric ischemia resulting from gastric conduit creation is associated with the development of anastomotic complications, suggesting that OFS is useful for assessing changes in conduit oxygenation during esophagectomy. Further studies are needed to refine this technology and investigate the clinical utility of intraoperative conduit oxygenation data.

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Esophagectomy with gastric pull-up reconstruction is associated with considerable morbidity of 40% to 50%, with anastomotic leak occurring in up to 20% of cases [1–10]. Ischemic changes in the proximal gastric conduit resulting from impaired arterial inflow and venous drainage has been implicated in the high anastomotic leak rate [11–16]. Postmortem examination of esophagectomy patients has demonstrated that the proximal 20% of a gastric conduit is perfused through a microscopic network of capillaries and arterioles [11]. This reliance on microcirculation for perfusion of the proximal gastric conduit makes it susceptible to ischemic injury.

A rapid and reliable method of assessing changes in gastric conduit perfusion is needed to investigate the pathophysiology of esophagectomy-associated anastomotic complications because the current clinical tools for the determination of visceral perfusion are limited in applicability and sensitivity. The two most commonly utilized modalities, Doppler ultrasound and intravenous fluorescein dye, demonstrate at-best sensitivity of 60% for the detection of ischemic bowel [17]. Spectral analysis can determine oxygen saturation in blood by measuring spectral shifts between unbound and oxygen bound hemoglobin molecules. Optical fiber spectroscopy has accurately assessed tissue oxygenation and blood content using this principle in an animal model of gastrointestinal ischemia as well as in patients with mesenteric ischemia [18, 19].

We hypothesize that the degree of relative gastric ischemia after gastric conduit creation is associated with the subsequent development of anastomotic complications after esophagectomy. The primary aim of this pilot study was to assess changes in gastric conduit perfusion during minimally invasive esophagectomy (MIE) using optical fiber spectroscopy. We also sought to determine whether intraoperative ischemic changes measured by

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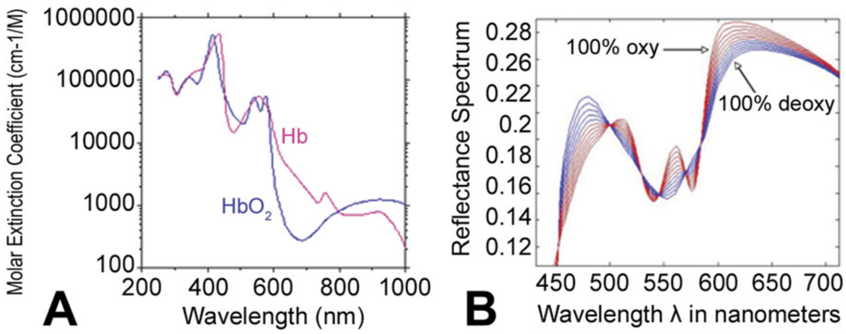

Fig 1. (A) Hemoglobin absorption spectrum. The molar extinction coefficient is directly proportional to the absorption coefficient. (B) The reflectance spectrum is predicted for tissue with a constant background scattering and blood content and varying absorption due to a set of oxygen saturation values ranging from 100% deoxygenated to 100% oxygenated.

optical fiber spectroscopy during gastric conduit formation are predictive of postoperative anastomotic complications in patients undergoing MIE.

Patients and Methods

Patients

Twenty-three patients were enrolled in our optical fiber spectroscopy study and underwent MIE with cervical or intrathoracic esophagogastrostomy between September 2008 and August 2009. Data were collected under a protocol approved by the Institutional Review Board of Oregon Health and Science University and are maintained in a prospective database. Data collected include patient characteristics, operative technique, gastric conduit tissue mixed arteriovenous oxygen saturation (Sa_{O_2}), relative tissue blood content, and anastomotic complications.

Optical Fiber Spectroscopy

The spectroscopic analysis utilizes the spectra of oxyhemoglobin and deoxyhemoglobin shown in Figure 1. The hemoglobin molecule exhibits interesting absorption properties in the visible light wavelength range, particularly the 5 isobestic points within the 480 to 700 nm wavelength range. At these wavelengths, HbO_2 (oxygenated hemoglobin) and Hb (deoxygenated hemoglobin) exhibit identical absorption. The slopes of the measured diffuse reflectance spectra about these isobestic points are linearly related to the oxygen saturation. Figure 1 shows the absorption coefficient of HbO_2 and Hb of blood (left) and a close up (right) of the 450 to 700 nm wavelength range used for analysis of optical measurements. An analysis module was developed based on the modified optical diffusion theory, which incorporates both the tissue scattering properties and blood absorption to enable specification of the blood volume fraction and the oxygen saturation of hemoglobin in the mixed arteriovenous vasculature.

Intraoperative optical fiber spectroscopy measurements were taken by passing the tissue probe through a laparoscopic trocar and placing it in direct apposition with the gastric serosa at a point on the proximal gastric fundus in the region of the proposed esophagogastric anastomosis. This area was marked with a suture to ensure consistent measurements. The laparoscopic light source was turned off during data collection to eliminate interference with spectroscopic readings. For each discrete measurement described below, five independent recordings were taken at each of three adjacent locations in the region of the anastomosis and averaged.

Operative Technique and Data Collection

In four patients, ischemic conditioning of the gastric conduit by division of the short gastric vessels was performed during staging laparoscopy with jejunostomy tube placement. Patients were selected for staging laparoscopy if radiographic staging demonstrated findings suspicious for metastatic disease. Staging laparoscopy was performed at least one week prior to definitive esophagectomy.

During MIE, gastric mobilization and conduit creation were performed with the patient in the supine, split legged position. After initial abdominal exploration, a marking stitch was placed at the superior margin of the greater curvature near the anticipated tip of the gastric conduit, and baseline spectroscopy measurements were obtained. The dissection began with the hiatal dissection, division of the short gastric vessels, and mobilization of the posterior stomach. A second set of spectroscopy measurements was taken after division of the short gastric vessels and mobilization of the greater curvature. A complete Kocher maneuver was performed to allow mobilization of the pylorus to the level of the esophageal hiatus. After complete gastric mobilization, the left gastric artery and coronary vein were divided near the base of the left gastric artery with a vascular stapler and a third set of spectroscopy measurements was obtained. A 4 to 5 cm wide stapled gastric tube was created, beginning along the lesser curve 6 cm proximal to the pylorus. A fourth set of measurements was obtained upon completion of the gastric conduit, and the final measurements were taken after transposition of the gastric conduit into the neck or chest.

Statistical Analysis

Data were analyzed using SPSS (version 15.0; SPSS Inc, Chicago, IL). Both oxygen saturation and blood volume fraction data were normalized to their respective baselines. Data were tested for normality and presented as mean ± standard deviation. Between-group comparisons of spectroscopy data were made using the Student *t* test,

Table 1. Patient Characteristics

Total number of patients	23
Age (years), mean ± SD	63 ± 10.5
Gender (male:female)	17:6
ASA classification, no. (%)	
1–2	4 (17)
3–4	19 (83)
BMI, kg/m^2, mean ± SD	28.3 ± 7.2
Tumor histology, no. (%)	
Adenocarcinoma	22 (95)
Squamous	1 (5)
Clinical staging, no. (%)	
Stage I	3 (13)
Stage II	6 (26)
Stage III	14 (61)
Type of MIS esophagectomy, no. (%)	
Transhiatal	4 (17)
Ivor-Lewis	5 (22)
3-field	14 (61)
Anastomotic complications, no. (%)	
Leaks	6 (26)
Strictures	3 (13)
Patients undergoing ischemic conditioning, no. (%)	4 (17)
Median duration of ischemic conditioning, days (range)	94.5 (8–210)

ASA = American Society of Anesthesiologists; BMI = body mass index; MIS = minimally invasive surgical; SD = standard deviation.

and within-group comparisons were made using the paired *t* test.

Results

Twenty-three patients underwent MIE for esophageal cancer with laparoscopic gastric conduit creation and assessment of gastric conduit perfusion using optical fiber spectroscopy. Patient characteristics are outlined by operative approach in Table 1. Overall, the average age was 63 ± 10 years, and 17 (74%) patients were males. All esophageal resections were performed for esophageal cancer with the vast majority for adenocarcinoma (95%). Five (17%) patients underwent Ivor-Lewis esophagectomy with intrathoracic esophagogastrostomy, whereas 18 (78%) had transposition of the gastric conduit to the neck with cervical esophagogastric anastomoses.

Significant changes in Sao_2 and blood volume fractions compared with baseline were observed during gastric conduit creation (Table 2). The Sao_2 decreased by 11% after division of the short gastric vessels ($p = 0.01$), 25.1% after division of left gastric vessels ($p < 0.01$), and 29.4% after gastric conduit creation ($p < 0.01$). Tissue blood volume fraction increased with successive division of the short gastric, left gastric, and conduit completion, but these increases did not reach statistical significance. However, after transposition of the gastric conduit blood volume fraction increased by 53% above baseline ($p < 0.01$), and Sao_2 returned to baseline levels.

A total of eight patients developed anastomotic complications (6 leaks and 3 strictures) with one of the eight having a leak with subsequent stricture at one month postoperative. When compared with the baseline Sao_2 measurements, patients with anastomotic complications exhibited significant reductions in Sao_2 after conduit creation ($p < 0.01$) and pull-up ($p < 0.01$). In contrast to patients without anastomotic complications, the drop in Sao_2 did not return to near baseline levels when the conduit was pulled up for the esophagogastric anastomosis. In addition, blood volume fraction was not significantly changed from baseline even after conduit translocation for the anastomosis (Table 3). There was a mean decrease in Sao_2 of 52.5% from baseline ($p < 0.01$) after construction of gastric conduit in patients who developed anastomotic complications compared with 15.1% in those that did not ($p = 0.01$). Blood volume fraction tended to be higher in patients without anastomotic complications as compared with patients with complications, but these differences were not statistically significant.

Four patients underwent ischemic conditioning by division of the short gastric vessels during staging laparoscopy at a median of 94.5 days prior to definitive esophagectomy. These patients did not experience significant changes in Sao_2 or blood volume fraction from baseline after conduit creation ($p = 0.72$ Sao_2, $p = 0.98$ blood volume fraction) and pull-up ($p = 0.40$ Sao_2, $p = 0.22$ blood volume fraction). Patients undergoing ischemic conditioning did not experience postoperative anastomotic complications. Comparing Sao_2 and blood vol-

Table 2. Tissue Mixed Arteriovenous Oxygen Saturation and Blood Volume Fraction Changes During Gastric Conduit Creation as a Percentage of Baseline Measurements

Time Point	% Oxygen Saturation (Mean ± SD)	p Value[a]	Blood Fraction Volume (Mean ± SD)	p Value[a]
Division of short gastric vessels	89.0 ± 18.9	0.01	1.10 ± 0.59	0.43
Division of left gastric vessels	74.9 ± 26.4	<0.01	1.29 ± 0.56	0.09
Completion of conduit	70.6 ± 38.9	<0.01	1.28 ± 0.66	0.06
Pull-up	90.1 ± 16.0	0.36	1.53 ± 0.60	<0.01

All values were normalized to respective group baseline measurements.

[a] Unpaired two tailed *t* test.

SD = standard deviation.

Table 3. Tissue Mixed Arteriovenous Oxygen Saturation and Blood Volume Fraction Changes in Patients With Anastomotic Complications Compared With Patients Without Anastomotic Complications

	% Oxygen Saturation (Mean ± SD)[a]			Blood Volume Fraction (Mean ± SD)[a]		
Anastomotic Complication	No	Yes	*p* Value[b]	No	Yes	*p* Value[b]
Short gastric vessel division	83.7 ± 22.2	97.6 ± 6.4	0.05	1.13 ± 0.67	1.06 ± 0.46	0.79
Left gastric vessel division	75.7 ± 32.3	73.5 ± 10.4	0.81	1.32 ± 0.59	0.99 ± 0.45	0.16
Completion of conduit	84.9 ± 42.2	47.5 ± 16.8	0.01	1.46 ± 0.72	0.99 ± 0.46	0.08
Pull-up	100.0 ± 52.3	71.1 ± 22.6	0.06	1.64 ± 0.61	1.34 ± 0.56	0.25

[a] All values were normalized to respective group baseline measurements. [b] Paired two tailed *t* test.

SD = standard deviation.

ume fraction in patients who underwent ischemic conditioning to those that did not, conditioned conduits showed a nonsignificant trend toward higher Sa_{O_2} and lower blood volume fractions (Table 4). Finally, Sa_{O_2} and blood volume fraction did not differ significantly in patients who had intrathoracic versus cervical anastomosis, $p = 0.29$ Sa_{O_2} and $p = 0.69$ blood volume fraction.

Comment

The central aims of this study were to examine the utility of optical fiber spectroscopy for assessing changes in gastric conduit perfusion during minimally invasive esophagectomy and to examine the relationship between intraoperative ischemic changes within the distal gastric conduit and the subsequent development of anastomotic complications. We demonstrated that optical fiber spectroscopy is a reliable method of assessing conduit oxygenation, and that marked changes in gastric fundus perfusion occur during gastric devascularization and conduit transposition. Patients with postoperative anastomotic complications had significant gastric conduit tip ischemia as measured by optical fiber spectroscopy, and demonstrated dramatic decreases in oxygen saturation after gastric conduit creation. Conversely, patients who underwent ischemic conditioning did not experience significant decreases in oxygen saturation or increases in blood content after gastric conduit creation. Finally, transposition of the stomach to the cervical location produces a significant increase in tissue blood content, likely due to venous congestion.

This study demonstrates significant decreases in tissue oxygenation after devascularization of the stomach and gastric tube creation, and the magnitude of this ischemia was associated with an increased rate of postoperative anastomotic complications. These results support the concept that relative ischemia at the tip of the gastric tube represents a major contributing factor in the development of anastomotic leak and stricture. Laser Doppler flowmetry has demonstrated significant decreases in blood flow to the distal gastric conduit after division of the short and left gastric vessels in patients undergoing esophagectomy [12, 14, 20]. These studies have also noted an association between gastric conduit perfusion and anastomotic complications; however, these small studies were not sufficiently powered to generate reliable sensitivity and specificity analysis. Also, laser Doppler flowmetry requires pulsatile blood flow, multiple measurements, and direct tissue contact which may alter local blood flow. These disadvantages, combined with the lack of data on the sensitivity and specificity for laser Doppler flowmetry, have limited its routine use for intraoperative assessment of visceral perfusion.

In this series, patients undergoing gastric ischemic conditioning did not did demonstrate significant changes in conduit oxygen saturation or blood content and none developed postoperative anastomotic complications. Although not statistically significant, patients who underwent ischemic conditioning had 20% higher oxygen saturation and lower blood volume content after conduit formation and pull-up compared with patients who underwent immediate reconstruction. These trends suggest an inflow and outflow effect from neovascularization. One recent study [21] did not detect any difference in

Table 4. Tissue Mixed Arteriovenous Oxygen Saturation and Blood Volume Fraction Changes in Patients After Gastric Ischemic Conditioning Compared With Patients Without Ischemic Conditioning

	% Oxygen Saturation (Mean ± SD)[a]			Blood Volume Fraction (Mean ± SD)[a]		
Ischemic Conditioning	No	Yes	*p* Value[b]	No	Yes	*p* Value[b]
Short gastric vessel division	88.6 ± 19.7	92.9 ± 11.2	0.69	1.10 ± 0.61	1.10 ± 0.28	0.99
Left gastric vessel division	74.4 ± 26.3	77.4 ± 31.0	0.86	1.25 ± 0.59	0.96 ± 0.34	0.22
Completion of conduit	67.8 ± 37.7	87.8 ± 50.6	0.57	1.33 ± 0.66	0.99 ± 0.73	0.50
Completion of anastomosis	80.7 ± 28.6	100.0 ± 82.4	0.25	1.56 ± 0.62	1.41 ± 0.53	0.63

[a] All values were normalized to respective group baseline measurements. [b] Paired two tailed *t* test.

SD = standard deviation.

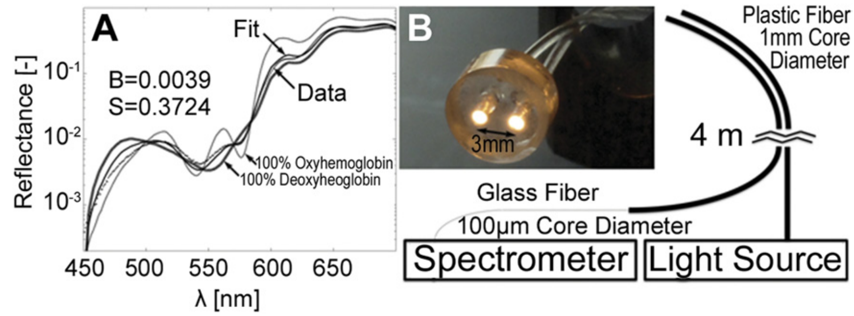

Fig 2. (A) A sample spectrum is specified by the fitting parameters: blood volume content (B), oxygen saturation (S = HbO_2/[Hb + HbO_2]). The Fit curve curve shows the predicted reflectance spectrum for the blood content and saturation. (B) The probe tip illuminated with white light in both emission and collection fibers for illustration. The block diagram shows the experimental setup. (Fit curve = lease square regression multidimensional unconstrained nonlinear error minimization [Nelder-Mead type].)

anastomotic complication rate between patients undergoing ischemic conditioning by short and left gastric vessel division performed 4 to 5 days prior to esophagectomy compared with those who did not. However, animal studies of gastric conduit ischemic conditioning [22, 23] indicate that a period of 14 to 28 days may be required to allow conduit perfusion to return to baseline levels. Thus, an ischemic conditioning time of 4 to 5 days may not be sufficient to produce significant improvement in gastric conduit perfusion. The median ischemic conditioning time in our study was 94 days, which was beyond the period of time required for neovascularization and reperfusion; however, the small number of patients who underwent ischemic conditioning precludes achieving statistical significance when compared with nonconditioned patients in this analysis.

This study demonstrates the feasibility of light spectroscopy for intraoperative assessment of visceral perfusion. Optical fiber spectroscopy provides a rapid and reliable method for collecting tissue perfusion data during laparoscopic and open surgery, and this technology offers significant benefit over any existing techniques. Whereas current systems are calibrated based on idealized curves, optical fiber spectroscopy performs dynamic measures that are repeatedly calibrated in vivo, adjusting to the actual physiologic parameters within tissue which provides more accurate measurements of tissue oxygen saturation and blood content. The laparoscopic probes are easily manipulated using standard laparoscopic instrumentation, and data acquisition requires less than one second (Fig 2). It should be emphasized that operating room lights (open or laparoscopic) must be turned off during data collection to prevent interference with the spectral analysis.

The potential to determine the degree of intraoperative ischemia that markedly increases the risk of postoperative anastomotic complications can facilitate development and assessment of preventative strategies such as stenting or delayed anastomosis [24–26]. The use of endoscopically placed removable covered stents for the successful management of postoperative leaks in patients undergoing esophagectomy has been reported [24, 25]. Although prophylactic stenting has not been reported for ischemic conduits, stents could be placed intraoperatively if the conduit shows evidence of ischemia by spectroscopy. The stents can be endoscopically removed once the anastomosis has healed. Alternatively, Oezcelik and colleagues [26] have described delayed esophagogastrostomy as a viable strategy for managing ischemic conduits.

This study is limited by its retrospective design, small sample size, and the inability to perform real-time assessment of gastric conduit perfusion intraoperatively. The relatively small number of patients hampered our ability to develop accurate receiver operating curves to determine threshold sensitivities and specificities for anastomotic complications using optical fiber spectroscopy. Ongoing intraoperative data collection to expand this cohort will allow this type of analysis in the future. A significant technical limitation of the current system is that the collected data can only be analyzed post hoc, and cannot be used to guide real-time decision making. In addition to providing a clinically useful assessment tool, the development of software to provide real-time data analysis and information regarding tissue oxygenation will allow for a more rigorous assessment of inter-user variation in measurement, and the effect of pressure on the tissue and the degree of tissue apposition on the measurements obtained. Another important limitation of the current study is that optical fiber spectroscopy was done only on the serosal surface of the gastric conduit. Studies that have used optical fiber spectroscopy have demonstrated that ischemic changes can be measured on both the serosal and mucosal surfaces [27–29]. However, none of the studies have shown that measurements taken on the serosal or mucosal surface were superior to the other for predicting anastomotic complications. Software development and further validation of the probe itself are required prior to introducing this technology more broadly for patient evaluation.

Intraoperative optical fiber spectroscopy can be used to assess gastric conduit perfusion during esophagectomy and it demonstrates a wide range of alterations in gastric conduit perfusion during esophageal replacement. The degree of gastric conduit ischemia was associated with the development of anastomotic complications. Gastric ischemic conditioning decreases the magnitude of ischemia seen after conduit creation; however, the relationship of these changes to the subsequent development of anastomotic complications remains unclear. Optical fiber spectroscopy provides a valuable tool to examine these relationships, and may prove useful for evaluating strategies designed to reduce ischemia-related complications such as ischemic preconditioning and augmentation of conduit arterial inflow.

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INVITED COMMENTARY

This study by Pham and colleagues [1] describes an intraoperative method to assess gastric conduit perfusion during minimally invasive esophagectomy. The technique, intraoperative optical fiber spectroscopy (OFS), works in a fashion similar to the familiar oxygen saturation probe to determine the oxygenation of the blood within the stomach graft. Although used during minimally invasive esophagectomy in this study, OFS could be used during open esophagectomy as well. The authors found that decreased gastric conduit perfusion, as mea-

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