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ARTICLE

Endoluminal Vacuum Therapy for Ivor Lewis Anastomotic Leaks: A Pilot Study in a Swine Model

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Anastomotic leaks are a serious complication associated with Ivor Lewis esophagectomies. Endoluminal negative pressure vacuum devices create a possible treatment alternative to conventional surgical intervention. Ten pigs had an intrathoracic esophageal anastomosis with a 1-cm defect. The experimental group had the device placed intraoperatively across the defect, whereas the control group did not. Once treatment was completed, a contrast fluoroscopic study and necropsy was performed. All control pigs had contrast extravasation on fluoroscopy and contamination on necropsy. The experimental group had no radiologic leak and no contamination on necropsy. The *P* value for leak is 0.03. This study demonstrated that endoluminal negative pressure vacuum therapy is tolerated in the swine model and is successful in facilitating the healing of anastomotic leaks. Endoluminal negative pressure vacuum therapy has potential clinical benefits, including decreased morbidity and length of hospital stay.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Negative pressure vacuum devices have been utilized in medicine for a variety of disease processes. The concept of an endoluminal device, while being utilized in Europe, is novel to the United States.

WHAT QUESTION DID THE STUDY ADDRESS?
✔ In this study, we evaluated whether the placement of an endoluminal negative pressure vacuum device across an esophageal anastomotic defect would facilitate healing in a swine model.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ An endoluminal negative pressure vacuum device is both safe and effective in facilitating the closure of anastomotic defects.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ Classically, esophageal anastomotic leaks are treated with drainage, diversion, and possible stent insertion requiring multiple interventions. Transitioning this device from swine to human trials could potentially decrease patient morbidity if used prophylactically in high-risk patients and decrease hospital cost and length of stay if multiple surgical interventions are avoided.

Esophageal cancer remains the sixth most common malignancy worldwide and is estimated to account for 16,000 deaths in the United States alone in 2015.[1] Patients without locally advanced or metastatic disease who are deemed good operative candidates can benefit from esophagectomy.[2]

The most common surgical options for esophageal cancer include either a transthoracic or a transhiatal esophagectomy.[3] In Western countries, transthoracic esophagectomies are performed more commonly secondary to the increased prevalence of adenocarcinoma in the lower one third of the esophagus as compared with squamous cell carcinoma, which is the most common esophageal cancer worldwide.

The complications associated with a transthoracic esophagectomy, also known as an Ivor Lewis esophagectomy, include, but are not limited to, cardiac arrhythmias, pneumonia, atelectasis, pulmonary embolism, intrathoracic and/or intraabdominal hemorrhage, anastomotic leak, anastomotic stricture, and recurrent laryngeal nerve injury.[4] The overall perioperative morbidity rate ranges between 30% and 60%.[5] The most dreaded complication remains an anastomotic leak that can subsequently lead to mediastinitis, sepsis, reoperation, and possible death. Although the overall anastomotic leak rate is between 10% and 30%, the rate does drop to approximately 5% at "high volume" centers, which is described as surgeons who perform greater than six esophagectomies per year.[4] Drainage, stenting, and reoperation with diversion are some typical treatments of anastomotic leak. Anastomotic leak remains an important cause of postoperative morbidity and mortality, and an alternative treatment approach for intrathoracic anastomotic

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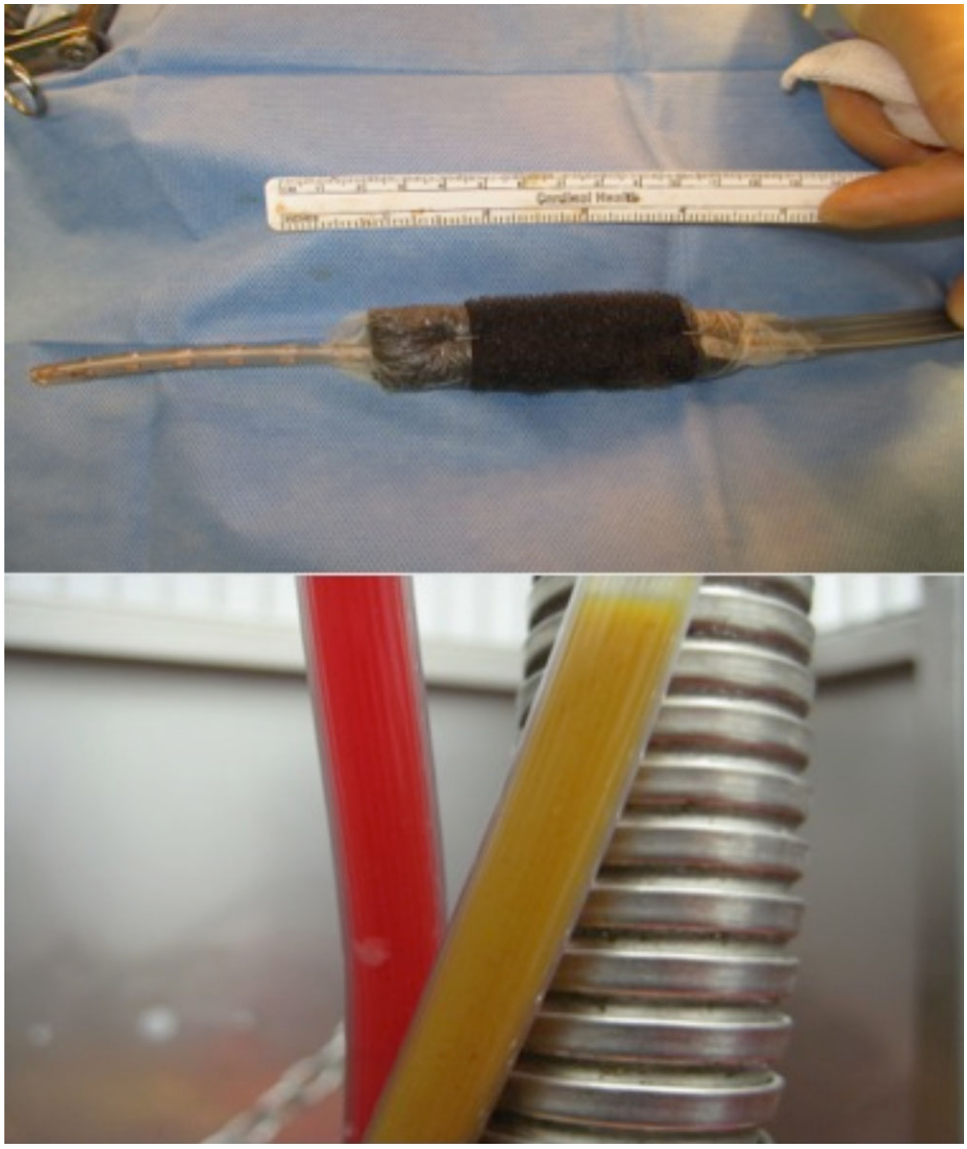

Figure 1 Top: Photograph of the negative-pressure device *ex vivo*, showing black Granufoam, adhesive moisture barrier, and sump and vacuum tubing. Bottom: Photograph of the external portion of the tubing system of the device, showing fluid drained by the vacuum sponge (red) and fluid from the proximal gastric sump (yellow-brown). Reprinted with permission from Surgical Infections 15/2, 2014, p.126, published by Mary Ann Liebert, Inc., New Rochelle, NY.

leaks as well as prophylactic measures taken in high-risk patients is warranted.

In our study, we use negative pressure wound therapy to facilitate the closure of anastomotic defects. Negative pressure wound therapy was introduced in the United States in 1995. The animal studies published in 1997 by Morykwas *et al.*[6] demonstrated negative pressure as a method to expedite wound healing by secondary intention of superficial wounds. Vacuum-assisted wound closure devices now have numerous clinical applications and have recently been utilized in the treatment of iatrogenic, postoperative, and spontaneous leaks of the esophagus in Germany and the United States with success.[7–13] The clinical implications of this type of device in treating esophageal anastomotic leaks is vast.

In this study, we investigate the feasibility of using an endoluminal negative pressure vacuum device to heal intentional anastomotic leaks in the thoracic esophageal conduit following an Ivor Lewis esophagectomy in a swine model. We have previously utilized this device in a swine low anterior resection model in both a prophylactic and salvage fashion, in which the anastomotic defects fully healed using the device.[14,15] We hypothesized that we would have comparable results using this device in an Ivor Lewis esophagectomy model to seal anastomotic leaks. This study is unique in that the device has not been readily utilized commercially in the United States and there are no other swine model studies besides our own to our knowledge. Additionally, our secondary endpoint was to evaluate mucosal integrity and inflammation at the anastomotic leak site.

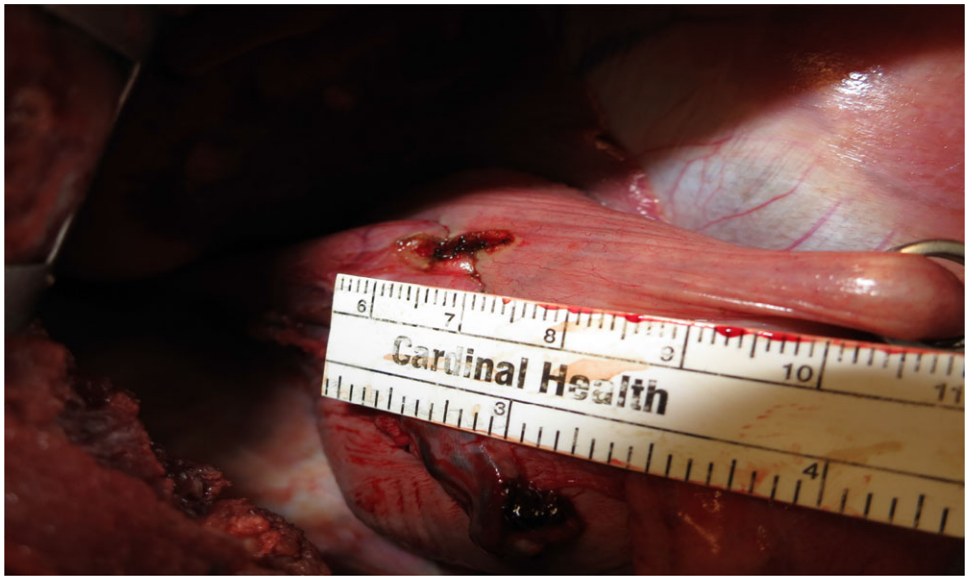

Figure 2 Photograph of the 1-cm intentional defect across the anastomosis with the experimental device in place. The control group had the same intentional defect without device placement.

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee at the University of Virginia approved this study.

Study design

Device description

The endoluminal vacuum device was created using black Granu-Foam (Kinetic Concept, San Antonio, TX) arranged around two 16-French nasogastric tubes (Bard Medical, Covington, GA). The distal tube was placed within the Granu-Foam to provide negative pressure to the sponge while the proximal tubing terminated in the proximal esophagus to suction secretions (**Figure 1**).[14,15]

Pig characteristics and operative preparation

All pig characteristics, operative preparation anesthesia, and postoperative care has been previously described and published.[14,15] Ten female Yorkshire pigs were utilized in this study. Upon arrival of the pigs to the vivarium, they were kept in standard husbandry conditions, fed a Teklad 7037 miniswine diet, and allowed to acclimate for 72 h prior to the initial operation.

Anesthesia and surgical approach

Prior to the beginning of the operation, the pigs were assigned to either the control or the experimental group. Anesthesia was conducted as previously described.[14,15] Throughout the operation, the pigs were monitored continuously with cardiopulmonary monitors and warmed with both a warm water-circulating bath and warm lactated Ringer's solution.

The neck, back, chest, and abdomen were shaved and the skin was prepped in a sterile fashion. An indwelling silastic catheter (0.062" inner diameter $\times$ 0.125" outer diameter) was placed in the internal jugular vein and tunneled subcutaneously to exit between the scapulae.

With the pig in the supine position, a vertical midline incision was made for access to the peritoneal cavity. The stomach and esophagus were identified and carefully mobilized to not disturb the vascular beds, which could possibly cause ischemia and/or necrosis. The proximal stomach was divided distal to the gastroesophageal junction with a linear stapling device. The distal aspect of the staple line would eventually become the gastric conduit. In order to ensure proper orientation, the distal staple line was gently sewn to the cut edge of the gastroesophageal junction to aid in pulling the conduit upward into the thoracic cavity along with the stomach later in the procedure.

The abdomen was then closed, and the pig was turned into the left lateral decubitus position. A posterior thoracotomy incision was made and the right side of the chest was entered utilizing a rib spreader. The esophagus was identified in the posterior mediastinum and dissected free from its attachments. At this point, the proximal stomach was released from the distal esophagus and a separate gastrotomy was made in the conduit to introduce a circular stapler. A segment of the distal esophagus, including the gastroesophageal junction, was then resected. The anvil was secured into the end of the esophagus and an end-to-end 21-mm circular anastomosis was completed between the esophagus and gastric conduit. A deliberate anterior 1-cm defect was then created across the circular staple line using cautery (**Figure 2**). With control subjects, the gastrotomy created for stapler introduction was closed with suture. A right-sided chest tube was placed and the right thoracotomy was closed. The first control pig did not have a chest tube placed but all subsequent pigs did.

In the experimental group, the esophagus was dissected out through a left-sided neck incision. A small esophagotomy was created and our endoluminal vacuum device (EVD)

was introduced into the esophagus and pulled into position with manipulation performed from the previously made gastrotomy. The device was positioned across the 1-cm anastomotic defect (**Figure 2**). The gastrotomy was closed with suture, as also done in the controls. The esophagotomy was closed around the EVD tubing with a purse-string suture. The EVD tubing was tunneled through the subcutaneous tissue and exited through the pig's back. The left-sided neck incision was closed with a passive Penrose drain sutured into the wound to aid in secretions draining freely from the wound onto gauze dressing. A right-sided chest tube was placed, the right posterior thoracotomy closed, and the operation was completed.

Postoperative care

All pigs were kept on a continuous low-dose Propofol infusion and supplemental oxygen during postoperative days 1 and 2, at which time they were safely weaned based on vital signs and observed subject comfort. Each pig had a right-sided chest tube kept on low continuous wall suction to collect pleural drainage.

For nutrition and hydration, continuous total parenteral nutrition and lactated Ringer's solution was administered via the central line. During the period between surgery and euthanasia, pigs were placed in a Lomir harness to prevent turning with a channel to protect i.v. and vacuum lines. In order to obtain vital signs and conduct a physical examination, the pigs were sedated as necessary with diazepam and acetylpromazine i.v. twice daily. In addition, the experimental pigs had their EVD suction and sump tubing placed to continuous suction to collect proximal and distal secretions. Pigs exhibiting signs of sepsis, peritonitis, or acute distress were removed from the study and euthanized humanely, according to the Institutional Animal Care and Use Committee protocol.

Macroscopic/fluoroscopic evaluation

On postoperative day 5, unless otherwise specified in the results, pigs were euthanized with Euthasol (Vibac), as previously described.[14,15] The EVD was removed at the end of the study and a postmortem upper gastrointestinal study with contrast (50% Hypaque diluted with water) was performed. At necropsy, the previous thoracotomy incision was opened and the thoracic cavity was examined for evidence of salivary contents, gastric contents, abscess, or phlegmon formation.

Histopathology

The esophageal anastomotic sites, uninvolved conduit, and any atypical appearing areas on macroscopic examination were excised and fixed in formalin. The sections were paraffin embedded, cut at 5-micrometer intervals with a standard microtome, and stained with hematoxylin and eosin. Each slide was evaluated by a single pathologist for mucosal integrity, inflammation, mucosal necrosis, and/or fibrinous adhesions. Inflammatory response was evaluated adjacent to the enterotomy site, and graded as mild, moderate, or severe, with mild representing increased mucosal inflammation, moderate representing increased inflammation with crypt loss, and severe demonstrating complete absence of crypts. Serositis was scored as mild if minimal serosal inflammation was present and moderate if inflammation and fibrinous adhesions were seen. Adhesions to any adjacent abdominal organs were recorded. A single pathologist evaluated each slide and was blinded as to which specimens came from control pigs vs. experimental pigs.

Table 1 Pig characteristics and necropsy/fluoroscopy results

Swine	POD euthanized	Cause of death	Fluoroscopy results	Necropsy results
Control #1[a]	0	Cardiopulmonary arrest	NA	NA
Control #2[a]	0	Cardiopulmonary arrest	NA	NA
Control #3[a]	0	Cardiopulmonary arrest	NA	NA
Control #4	5	Euthanized 2° to distress	Unsuccessful	Leak
Control #5	2	Found deceased	Leak	Leak
Control #6	1	Euthanized 2° to distress	Leak	Leak
Experimental #1	6	Completed study	No leak	No leak
Experimental #2	3	Researcher technical error	No leak	No leak
Experimental #3	7	Completed study	No leak	No leak
Experimental #4	5	Euthanized 2° to distress	No leak	No leak

NA, not applicable; POD, postoperative day.
[a]These pigs were not included in the final statistical analysis.

Statistical analysis

Fisher's exact test was performed using GraphPad Prism version 6.0f for Mac OS X, (GraphPad Software, La Jolla, CA; www.graphpad.com). A P value of < 0.05 was used to determine statistical significance.

RESULTS

Gross evaluation and fluoroscopy

Six pigs comprised the initial control group and did not undergo EVD placement. The first three subjects in the series died within 24 h of their operation. During the course of the study, we amended our protocol to include a postoperative chest tube, low dose i.v. continuous sedation, and oxygen delivered by nasal cannula to improve postoperative survival for the duration of the study. None of the controls survived to the planned postoperative day 5 secondary to distress (**Table 1**). All three controls either demonstrated a frank leak on fluoroscopy, or had gastric contents and/or phlegmon present in the pleural cavity on necropsy (**Figure 3**).

There were initially four pigs in the experimental group with placement of the EVD. One of the experimental pigs died on postoperative day 3. A postmortem fluoroscopic examination and necropsy was subsequently done on this pig and there was no leak evident from the anastomosis. The remaining three experimental pigs tolerated surgery and implantation of the device. They were euthanized on postoperative day 5 through 7 and all pigs showed complete closure of their esophagogastric anastomotic defect on postmortem

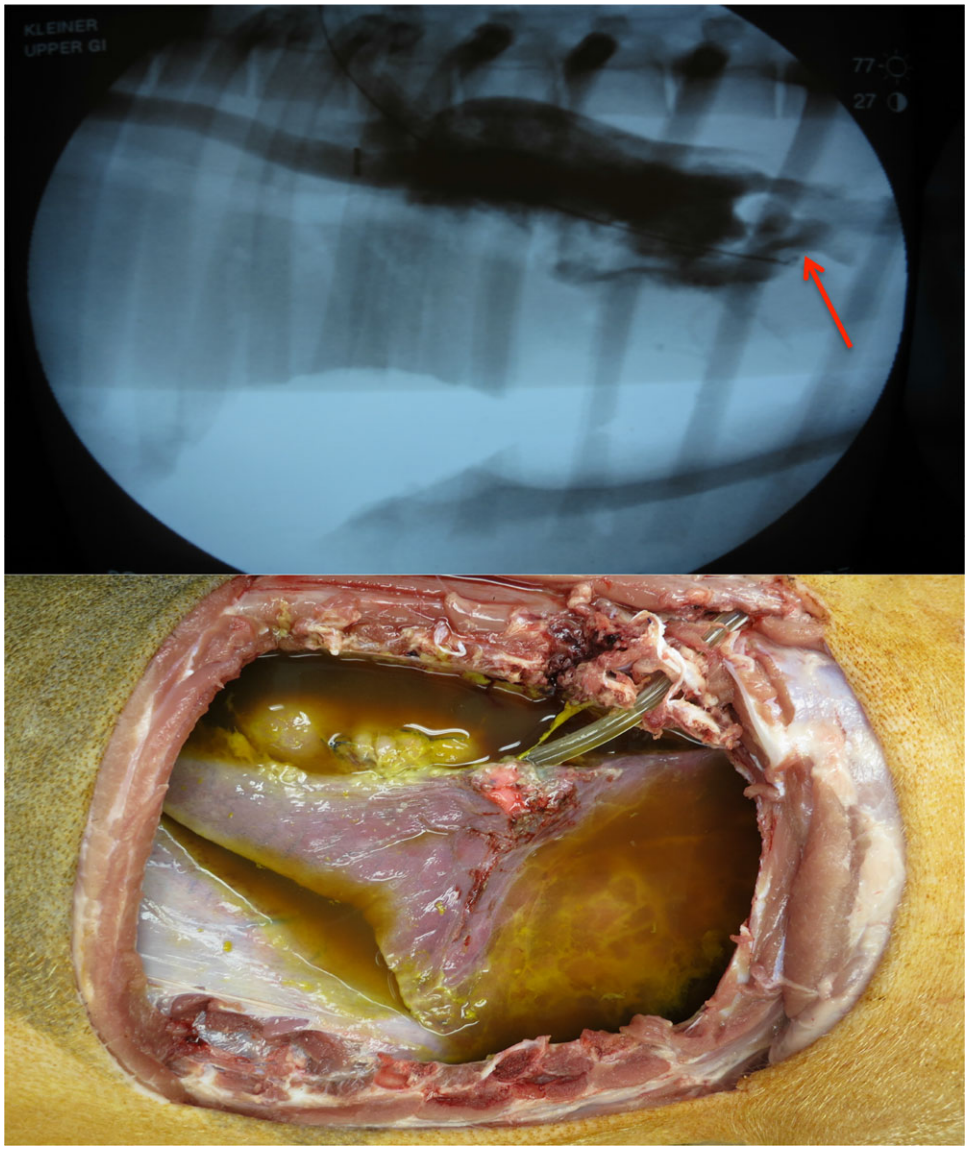

Figure 3 Top: Control fluoroscopy study at day 5 showing frank extravasation of contrast out of the anastomotic defect (arrow red). Bottom: Photograph of the control at necropsy demonstrating frank contamination of the thoracic cavity with gastric contents.

fluoroscopy (**Table 1**). On necropsy, there was no evidence of gross pleural contamination (**Figure 4**).

Statistical analysis

A *P* value for postoperative leak between the two groups using a Fisher's exact test was 0.03 (**Table 2**). The three control pigs that died within the first 24 h of surgery were not included in the statistical analysis.

Histology

All specimens from the control and experimental pigs were evaluated. Histologically, specimens from the experimental pigs trended toward having lesser degree of severe inflammation when compared with the control group; however, this was not statistically significant ($P = 0.14$). The degree of inflammation, serositis, adhesions, and ischemic tissue were scored for each specimen and are categorized in **Table 3**.

DISCUSSION

In our study, we assessed the use of an EVD as the sole treatment modality for closure of an intentional esophageal anastomotic defect after an Ivor Lewis esophagectomy in the swine model. In this study, as well as our previous low anterior resection model, endoluminal vacuum therapy is well tolerated and was successful in 100% of the experimental animals.[14] In this study, the intentional anastomotic defect was approximately one third of the diameter of the esophageal lumen and, after experimental treatment, is seen to be entirely healed on fluoroscopic studies and necropsy evaluation. Unlike the control group, none of the

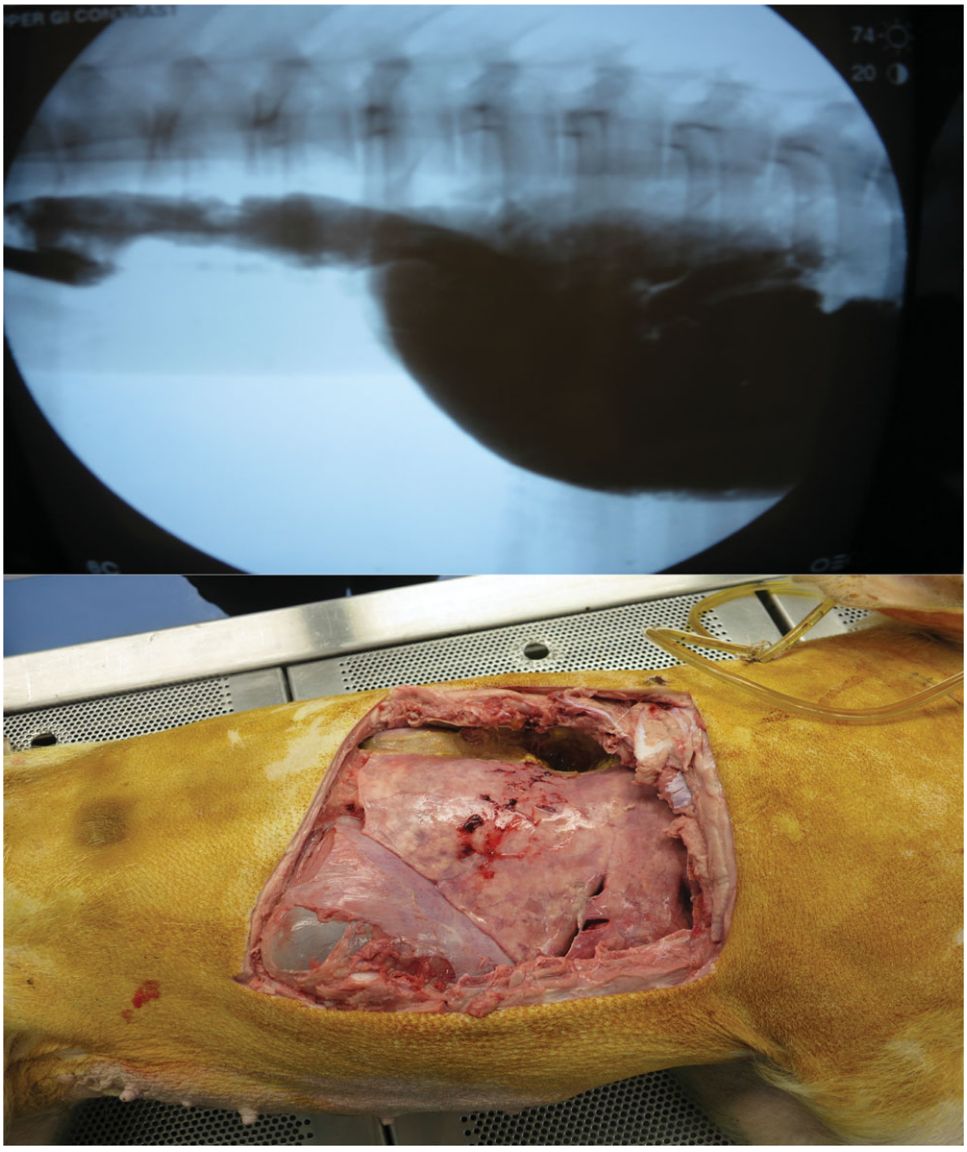

Figure 4 Top: Experimental fluoroscopy study at day 5 showing no extravasation of contrast at the site of the intentional anastomotic defect. Bottom: Photograph demonstrating the experimental thoracic cavity without contamination with gastric contents.

Table 2 Fluoroscopy and necropsy results

	Control $N = 3$	Experimental $N = 4$
Leak	3	0
No leak	0	4

The P value was calculated using Fisher's exact test; $P = 0.03$.

Table 3 Histological results

Group	Inflammation	Serositis	Adhesions	Necrosis/ Ischemia
Control	33% mild	66% none	34% fibrinous	17%
	66% severe	34% mild		
Experimental	100% mild	66% none	None	None
		34% mild		

experimental animals demonstrated signs of mediastinitis or sepsis during the postoperative period.

Half of the control animals died within 24 h of iatrogenic perforation, most likely from acute cardiopulmonary collapse, because swine are well known to have very little pulmonary reserve after thoracotomy. After the death of these three animals, the addition of a right-sided chest tube improved outcomes and was subsequently placed during all future procedures. Additionally, one experimental pig died due to researcher error in the postoperative period that was not related to the surgery or the device. The death was ultimately investigated by the Institutional Animal Care and Use Committee and was attributed to an inexperienced researcher placing the sedated subject too close to the heat source. Despite the small size in this study, the complete

resolution of leaks seen on all experimental animals is significant when compared with the controls. We attribute the lack of closure of the control group over the study period to the large size of the defect that represents a complete anastomotic breakdown.

One of the most devastating and well-researched complications after an Ivor Lewis esophagectomy continues to be an anastomotic leak. A retrospective study from the Society of Thoracic Surgeons Database identified the most common risk factors for leak after esophagectomy. The risk factors included obesity, coronary artery disease, hypertension, steroids, length of procedure >5 h, diabetes, renal insufficiency, and tobacco use. The anastomotic leaks are subsequently associated with atrial arrhythmias, increased risk of deep venous thrombosis, development of acute respiratory distress syndrome, reintubation within 24 h, reoperation, esophageal dilatation prior to discharge, and new onset renal failure. All of these complications greatly affect patient's quality of life, length of stay in the hospital, and cost of hospitalization and future medical and surgical interventions.[16]

With this study, we have shown that 5 days of endoluminal negative pressure therapy assists in the perioperative closure of anastomotic leaks that would not close without other surgical or endoscopic intervention. The use of this device could have two direct implications for the care of such patients. It could provide a way to manage anastomotic leaks without reoperation, diversion, and a second stage surgery for reconstruction. This would potentially improve a patient's quality of life and decrease hospital cost. Second, this device could be placed prophylactically in patients recognized to be at high risk for an anastomotic leak in an attempt to prevent anastomotic dehiscence.

As alluded to earlier, previous studies have evaluated the use of endoluminal negative pressure wound therapy devices in healing esophageal anastomotic leaks with some success when used in conjunction with esophageal stents. Our study looks at using the endoluminal therapy as a sole therapy for use in such leaks in the swine model. Some limitations of this study are that it did not look at the long-term outcome of using this device in healing anastomotic leaks. In order to assess the durability of these anastomoses after removal of the negative pressure device, follow-up survival studies would be necessary. Additionally, we did not study the use of the device in a contaminated and inflamed field to mimic an acute postoperative leak. We did demonstrate its potential beneficial use in prophylaxis as we previously demonstrated in our rectal series.[14] Given all of the accumulated data, we propose that a human safety and efficacy trial could be initiated in the near future.

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Conflict Of Interest. A.L.S. and L.A.R. received financial salary and funding for academic travel support from senior author, D.E.K. Authors R.B.S. and S.H.F. have no conflicts of interest or funding sources to disclose. The senior author, D.E.K., is the inventor of the described device and currently has a patent for this technology. At some point in the future, he may have financial benefit for this device. There is no sponsoring company or financial agreements for this work.

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