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Review Article

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Gastroesophageal reflux disease (GERD) can be one of the most distressing conditions developing at different ages in infants and children. The disease itself is a complex process along with ongoing dynamic anatomic and physiologic changes occurring during normal development. Therefore among referring physicians, considerations regarding the role of surgery for GERD in children varies widely depending on individual experiences in managing these patients. These varied opinions result in discrepancies in the operative experience with fundoplication among pediatric surgeons. It is unclear how much of the current opinions stem from published evidence, particularly with regard to the safety and efficacy of the current operative techniques. Therefore, in this review, the literature regarding the disease process as well as our personal experience with anti-reflux operations will be reviewed.

Natural History

Gastroesophageal reflux occurs in varying degrees in the majority of infants. Reflux to the degree of at least 2 episodes per day during the first 4 months of life is common enough to be considered normal or physiologic. Emesis during this time has been termed chalasia and occurs in about 70% of infants around 3 months of age. Development of anti-reflux barriers usually occurs during the first year of life causing resolution of symptoms in most of these patients. This incidence of GER often drops to 5% by age 1 year with the greatest decrease in symptoms occurring between 6 to 8 months of age.[1,2,3] In patients who continue to display symptoms after 18 months of age, pathologic reflux extending into adulthood is more likely.[3,4] Pathologic reflux persists beyond 2 years of age in some, but the manifestations change to more subjective symptoms, and evidence from a large cross-sectional cohort study has shown these patients are generally undertreated.[5]

Development of the Anti-Reflux Barrier

During the first year of life, the lower esophagus sphincter (LES) undergoes post-natal development that contributes to competency.[6,7] The LES represents the terminal portion of the inner circular muscle layer of the esophagus. This muscle layer is thickened which contributes to the high pressure zone and extends onto the lesser curvature of the stomach.[8] The phrenoesophageal membrane, arising from the septum transversum, holds the LES in position which is important for the normal barrier function against GERD. This point can be identified manometrically by demonstrating the point of respiratory inversion between the thoracic esophagus and abdominal esophagus. The length of intra-abdominal esophagus is also important. There is a relatively shorter length of intra-abdominal esophagus at birth which gradually elongates over the next several months. During this time, the pressure gradient generated by the LES increases which promotes a more competent barrier against reflux.

In adults, LES pressures greater than 30 mmHg have been shown to prevent reflux whereas pressures between 0 and 5 mmHg resulted in abnormal pH studies consistent with reflux in 80% of patients.[9] GERD is more likely to develop when the LES pressure is less than 6 mmHg at the respiratory inversion point, and the overall LES length is less than 2 cm, of which less than 1 cm is intra-abdominal.[10]

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This emphasizes the importance of the intra-abdominal length of esophagus. When abdominal length is more than 3 cm in adults and with normal abdominal pressure, there is LES competency in all patients, while a length of less than 1 cm results in significant reflux.[9] These data have led some surgeons to state that mobilization of an adequate length of intra-abdominal esophagus at the time of the fundoplication is necessary to prevent recurrent reflux. This assumption for infants and children is currently being challenged in a prospective trial that will be discussed later.

Another impediment to reflux is the existence of a normal acute angle of His.[11] Although the precise functional component of the angle of His is not well defined, when the angle is more obtuse, reflux is more likely. This is a possible explanation for why some patients develop worsening reflux following gastrostomy.[12,13] Accentuation of the angle of His inhibits reflux which is the main mechanism of action for anterior fundoplications (Thal, Dor, Hill, Boix-Ochoa).[14-18]

Normally, communication between the esophagus and stomach during peristalsis allows clearance of esophageal contents into the stomach, which is subsequently emptied before overdistension develops. Esophageal dysmotility, as seen in esophageal atresia and achalasia patients, contributes to GERD by decreased clearance. Delayed gastric emptying, seen more commonly in children with neurologic impairment, also promotes GERD because of the delay in the evacuation of gastric contents. However, the role of delayed gastric emptying in early childhood reflux is not clear since infants with more severe reflux have been shown to have faster gastric emptying. Moreover, gastric emptying has been shown to improve following Nissen fundoplication. Finally, esophageal motility is important to study prior to an antireflux procedure in adults but is rarely necessary in children without a pre-existing history of a smooth muscle disorder.

LES relaxation occurs normally with esophageal peristalsis, resulting in comfortable passage of food to the stomach. Separate from the mechanistic issues discussed above, inappropriate LES relaxations, including when the stomach is full, have been shown to occur sporadically. These are called transient LES relaxations (TLESRs). TLESRs are suspected to be part of the mechanism for gastroesophageal reflux in adults and children.[19-22]

In summary, a short LES length, an obtuse angle of HIS, esophageal dysmotility, transient LES relaxations, and hiatal hernia with or without migration of the LES into the chest can contribute to failure of the LES resulting in gastroesophageal reflux.

Presentation

Clinical symptoms in infants and young children include frequent vomiting, food refusal, arching of the back with crying after feeding, frequent gulping and swallowing between feeding, and coughing between feeding and at night. These symptoms are often exacerbated when lying down. Complications of reflux include failure to thrive, weight loss, aspiration pneumonia and sometimes apnea/bradycardia events may cause life threatening events (ALTE). In addition, irritation of the pharynx can lead to stimulation of airway reflexes causing or exacerbating reactive airway disease.[22]

In the 3-17 year age range, the most common symptoms in decreasing frequency are epigastric discomfort, burning/pain in middle of chest, and sour taste.[23] These children may also present with esophagitis, strictures and, occasionally, Barrett's esophagus. Many adolescents have been managed medically for several years prior to referral for operative therapy. In children under age 5, cough, anorexia and feeding refusal occur more commonly when erosive esophagitis is present.[24]

Neurologic impairment is a frequent co-morbidity associated with gastroesophageal reflux in children. Neurologically impaired children often require a gastrostomy due to swallowing dysfunction. In this situation, particularly if the neurologic impairment is severe or associated with spastic contractions, a work-up for significant reflux should be considered.

Diagnosis

Patients are often evaluated with a contrast swallow study (upper GI study) prior to any other testing. This study outlines the baseline anatomy, identifying if a hiatal hernia or malrotation is present and whether or not there is an anatomic reason for reflux. However, as a study to define the presence or absence of pathologic reflux, a barium swallow is not an

adequate examination for the overall accuracy is no better than 50%.[25-27] Endoscopy is less utilized in children compared to adults. While it can diagnose mucosal complications of reflux, many children with severe reflux will have a negative examination thus producing a low sensitivity from this study.[22,23]

A 24-hour esophageal pH manometry records esophageal exposures under a pH of 4 and is believed by many to be the most accurate method of diagnosing acid reflux with the sensitivity and specificity reported to be greater than 90%.[27-31] In infants, the relative sensitivity and specificity often depends on how the normal/abnormal boundaries are set. A total percentage of reflux time (> 5.2%) has been shown to be an accurate means of diagnosing GERD in infants.[32] Recently it has also been reported that not all pathologic reflux in infants, including reflux causing aspiration and apneic events, is acidic in nature. [33,34] Therefore, the standard pH study is flawed in this population as it does not detect all episodes of relux.[35] Multi-channel intraluminal impedance monitoring addresses this concern by recording all episodes of reflux regardless of pH.[35,36] This test detects alterations in an electrical flow being measured throughout the length of the esophagus caused by any intra-esophageal contents. Thus, this study can delineate the proximal extent of reflux and the temporal association between reflux and symptoms. Moreover, when used with pH monitoring, it portrays a complete picture of the esophageal exposures.[36-38] While the future application of this technology seems apparent, its utility is currently limited until normal values are established in the pediatric population.[39, 40]

As previously mentioned, gastric emptying studies are not useful during routine preoperative evaluation since Nissen fundoplication accelerates gastric emptying.[41-43] The impact of delayed gastric emptying has previously been shown to have little influence on post-operative outcome.[42] However, recent results from a long-term quality of life study found that post-operative delayed gastric emptying predicted lower satisfaction even though the gastric emptying was improved over pre-operative values.[43] In this regard it is our practice to perform gastric emptying studies especially when there is a need for a second procedure to determine the necessity for pyloroplasty. On rare occasions when a third operation is required, we perform pyloroplasty routinely because of the likelihood that gastric dysfunction will occur if it does not already exist.

Indications for Surgery

As most infants with modest gastroesophageal reflux will not need an operation, indications for fundoplication in infants are considered carefully. These indications mostly involve patients in imminent danger from their disease such as infants exhibiting weight loss/growth failure, aspiration pneumonias, and/or presentation with an apparent life threatening event (ALTE).

The most common indication for fundoplication for infants in our hospital is an ALTE episode. Given the life-threatening nature of the event, we proceed to fundoplication rather than attempt medical management. In a recent report from our hospital, 78 of 81 patients undergoing fundoplication for ALTE between 2000 and 2005 were treated at some point with anti-reflux medication. Moreover, 71 (88%) were taking anti-reflux medication at the time of their admission for ALTE.[44] To clarify, this is not apnea of prematurity, for which data on the relationship with GERD is conflicting.[34,45] These ALTE patients typically are brought into the emergency room from home with a near death event. In this population, where the natural history for recurrent ALTE spells or mortality is not well documented, we have found excellent efficacy in preventing recurrent ALTE with fundoplication.[44]

For patients between two and five years of age, the most frequent indication is failure to maintain adequate growth, and for children older than 5 years, it is failure of medical management.

Neurologically impaired patients who require gastrostomy include all age groups and often present a management dilemma.[46-48] Due to their high risk for developing reflux, particularly after gastrostomy, many authors have felt a protective fundoplication is indicated routinely, or that all these patients should be evaluated for reflux even if they do not demonstrate symptoms.[49-51] However, recent evidence suggests that neurologically impaired patients requiring gastrostomy have a low incidence of subsequently requiring a fundoplication, even when a pH study is positive prior to the gastrostomy.[52-54] These data suggests only patients with active reflux symptoms prior to gastrostomy should be subjected to a fundoplication.

Operation for GERD

Although many variants exist, the main categories of fundoplication are partial and anterior (Boix-Ochoa, Thal, Dor), partial posterior (Toupet) and complete fundoplication (Nissen). In animal models, there is no functional difference between anterior, posterior or total fundoplication.[55] The only level one evidence on the topic is a prospective, randomized controlled trial in adults showing that partial posterior fundoplication is superior to partial anterior fundoplication.[56] A prospective, non-randomized evaluation between partial anterior and complete fundoplication in neurologically impaired children found no statistical difference in results or complications.[57] One retrospective series showed a partial anterior (Boix Ochoa) fundoplication to be superior in neurologically normal patients, but complete (Nissen) fundoplication to be superior in neurologically impaired patients.[58] However, these findings have not been validated by other centers.[59,60] A recent large series comparing laparoscopic Nissen, Toupet and Thal fundoplications in children found no difference in success or complications between any of the techniques.[60] In this study the authors found that most complications were related to the surgeon's early experience with the respective techniques. Given the published data on the type of fundoplication, it is currently clear that the choice of operation should be determined by the surgeon's experience and expertise.

Regardless of the type of fundoplication utilized, there is little controversy over the operative approach. All levels of evidence in children and adults have demonstrated that the laparoscopic approach offers less morbidity, more rapid recovery, better cosmesis and, at least, equal results.[61-72] With experience, the operation can be done with an operative time similar to the open approach.[71,72] While there were early concerns about the costs of the operation, the cost difference is usually nullified by the shorter recovery and treatment of complications offering resource advantages to laparoscopy.[73,74] In a recent report from our institution comparing charges for patients undergoing open and laparoscopic fundoplication, the total charges were similar although these charges differed depending on the approach[75] Table 1. At this time, we believe the open procedure should be reserved for those who possess a contraindication to laparoscopy.

Technical Considerations

Infants and small children have a thin abdominal wall which allows instruments to be passed directly through small stab incisions[76] (Fig. 1). This technique produces smaller incisions, more working room within a small abdominal cavity, and results in significant cost savings and shorter hospitalization with decreased discomfort.

When performing a Nissen fundoplication in infants and young children, the length of the fundoplication can be made at 2 cm for all patients with good results regardless of size[77] (Fig. 2). The functional diameter of the wrap should be size adjusted whereby the choice of bougie is based on body weight at operation. For patients less than 15kg, we have developed a table for the patient's weight and bougie size [77] Table 2.

Table 1. Factors favoring laparoscopic and open fundoplication in a group of 100 consecutive children undergoing fundoplication. Fifty children underwent laparoscopic fundoplication and fifty underwent open fundoplication.[75]

Favoring LF	P Value	Favoring OF	P Value
LOS (1.2 vs. 2.9 days)	<0.01	Operating Time (77 vs. 91 min)	0.03
Time to Initial Feeds (7.3 vs. 27.9 hrs)	<0.01		
Time to Full Feeds (21.8 vs. 42.9 hrs)	<0.01		
Equipment ($1006 vs. $1609)	0.003	Anesthesia ($389 vs. $475)	0.01
Hospital Room ($1290 vs. $2847)	0.004	Central Supply/Sterilization ($1367 vs. $2515)	<0.001
Pharmacy ($180 vs. $461)	0.01	Operating Suite ($4058 vs. $5142)	0.04

LOS = Postoperative length of hospitalization.

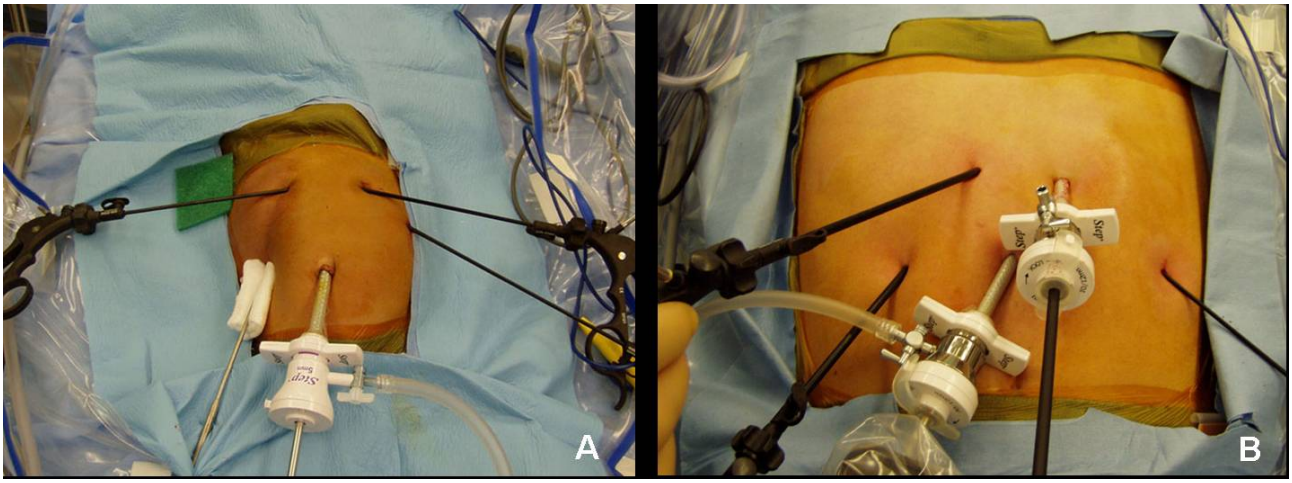

Fig. 1. We utilize the stab incision technique whereby instruments are introduced directly through the skin. In infants, a 5mm port is placed in the umbilicus through which the telescope is introduced. The instruments are then passed through the other four accessory sites through stab incisions (A). In adolescents two ports are initially introduced. A 5 mm port is inserted through the umbilicus and a 5mm port is placed in the patient's left epigastrium through which the ultrasonic scalpel is introduced (B). Notice the two instruments on the patient's right side in (B) are 5mm in size. The instrument in the patient's left epigastrium is 3mm in size.

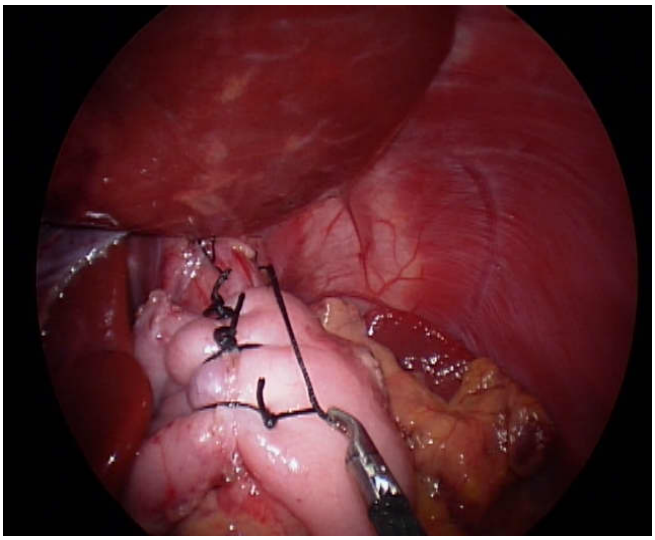

Fig 2. We always measure the length of the fundoplication, trying to perform a 2cm length wrap. In this photograph, the silk string alongside the three sutures has been cut to 2cm, indicating that the wrap is approximately 2cm in length.

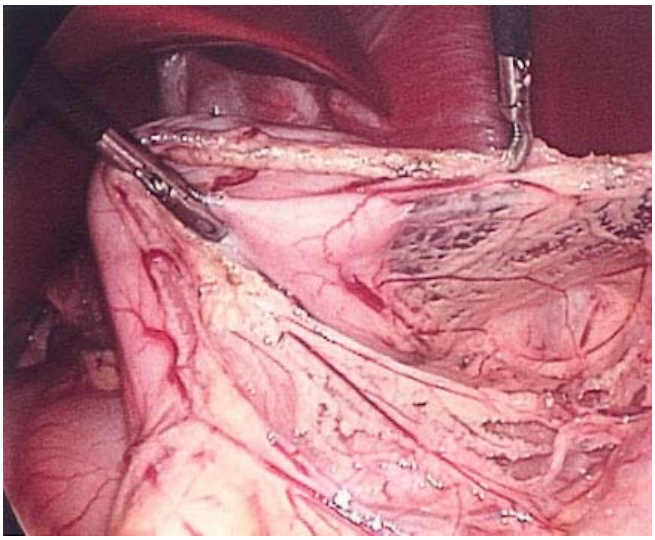

Fig 3. We believe that the short gastric vessels should be ligated and divided in all patients to fully mobilize the stomach for a loose, floppy Nissen. In this photograph, the short gastric vessels are being ligated and divided with the Maryland dissecting instrument connected to cautery. We utilize the Maryland dissecting instrument connected to cautery in most patients under 8-10 years of age. In older patients, we use the ultrasonic scalpel.

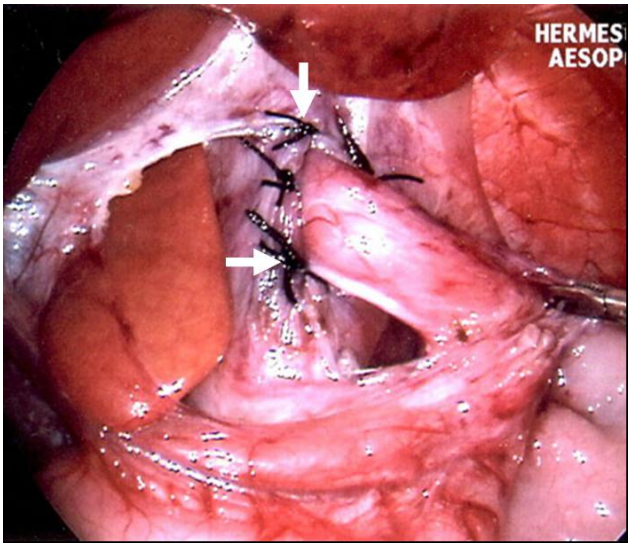

Fig 4. We have modified our fundoplication technique and place sutures securing the esophagus to the crura at the 7:00, 11:00, 2:00 and 5:00 positions. These sutures are seen in this particular photograph. Also seen is a suture (arrows) closing the crura both posteriorly and anteriorly. Note the vagus nerve as it resides along the posterior aspect of the esophagus.

Table 2. Recommended bougie size for esophageal calibration according to patient weight for babies less than 15kg undergoing laparoscopic fundoplication. Reprinted with permission.[77]

Weight (kg)	Bougie Size
2.5-4.0	20-24
4.0-5.5	24-28
5.5-7.0	28-32
7.0-8.5	32-34
8.5-10.0	34-36
10.0-15.0	36-40

The short gastric vessels can easily be obliterated with electrocautery in patients up to age 5 (Fig. 3). In older children, we typically utilize the ultrasonic scalpel. Preservation of the short gastrics has been reported without compromising results.[78] However; we believe that it is difficult to create a loose, floppy, Nissen without dividing the short gastric vessels for adequate mobilization of the stomach.

The most common major complication of the laparoscopic fundoplication is post-operative transmigration of the wrap through the esophageal hiatus and into the chest.[79-81] There is some evidence that this complication is more common with the laparoscopic operation, perhaps due to decreased gastric adhesions with laparoscopy.[82] Many authors have speculated mechanisms leading to surgical failures.[83-88] Decreased recurrence rates in the repair of large paraesophageal hernias with the use of mesh have been shown in adults,[89,90] leading some adult surgeons to employ a synthetic barrier when closing the crura during the primary laparoscopic fundoplication.[91-93] We have utilized a more simple technique to buttress the crural closure during the primary fundoplication. By placing four evenly distributed sutures between the esophagus and crura (Fig. 4), we have substantially reduced our rate of wrap herniation.[81] These esophago-crural sutures are placed to obliterate the space between the esophagus and crura.

Currently it is not clear whether the phrenoesophageal membrane should be incised, allowing complete mobilization of the distal esophagus in patients without a hiatal hernia. It is easy to speculate that not performing this dissection might help prevent herniation, decrease the chance of vagal injury, and perhaps maintain more inherent function of the LES. However, leaving the phrenoesophageal attachments in place violates long-standing surgical principles for treating reflux. As previously mentioned in adults, an appropriate length of intra-abdominal esophagus has been shown to be an important component of the lower esophageal barriers for preventing reflux.[9,11,94,95] This concept has led many surgeons to believe that complete esophageal mobilization is important to provide adequate intra-abdominal esophageal length. These concepts, however, have never been investigated in children. Moreover, recent evidence in adults has shown that minimal esophageal dissection can provide excellent control of reflux symptoms.[83,84] In a previously cited report, in addition to utilizing four esophago-crural sutures to obliterate the space between the esophagus and crura, we also employed minimal esophageal mobilization and found excellent functional results following these two modifications.[81] Moreover, we were able to reduce the incidence of wrap transmigration from 12% to 5%. We have begun a multi-institutional prospective randomized trial comparing extensive to minimal esophageal

mobilization which should in time help clarify this issue in children.

When wrap herniation occurs post-operatively, the crural repair at the second operation can be tenuous since these hiatal defects often have become quite large and the diaphragmatic edges are thin. Therefore, it might be expected that approximating these thin crural tissues together across a wide distance would predispose to an even higher recurrence rate following the second operation. This was true in our initial experience with the re-do operation. We have modified our re-do technique by reinforcing the crural repair with a biosynthetic mesh following approximation of the crura.[95] In our recent experience, recurrent transmigration of the wrap have developed only in patients in whom biosynthetic mesh reinforcement was not utilized.[95]

Outcomes

Results from laparoscopic anti-reflux operations are quickly outdated as most centers improve and refine their technique often before publications are received. Essentially, current techniques are all effective at controlling reflux symptoms. Recent series in neurologically normal children report over a 95% success rate for having patients free of symptoms at 5 year follow-up.[60,78] Similarly, a 21-center prospective series representing a wide range of technical experience with the operations in neurologically normal and impaired adults reported over 85% of the patients were symptom free at 5 years.[97] Neurologically impaired patients can be expected to have more complications after an operation due to their hypertonicity and the severity of preoperative reflux. In spite of this, recent series focused on this high risk population have demonstrated control of reflux in at least 85% of patients at 5 years.[98,100] However, these patients will have a much higher mortality rate (10-15%) during the post-operative period related to their other co-morbidities. [98,100] In a recently published series, intraoperative complications were found to occur in 5% of patients. All of these complications occurred during the early part of the authors' experience.[60] Since 2000, in our laparoscopic fundoplication experience, intraoperative complications have been extremely rare. The most significant post-operative complication and the only reason for re-do operation has been herniation of the fundoplication wrap into the chest. We have reduced our rate from 12% to 5% with the addition of the previously described esophago-crural sutures and minimal esophageal mobilization.[81] Moreover; we have not had a single patient develop wrap transmigration since 2004 when we began to routinely use four esophago-crural sutures to obliterate the space between the esophagus and crura.

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