Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia

Authors P. J. Pasricha[1], R. Hawari[1], I. Ahmed[1], J. Chen[1], P. B. Cotton[2], R. H. Hawes[2], A. N. Kalloo[3], S. V. Kantsevoy[3], C. J. Gostout[4]

Institutions
[1] Divison of Gastroenterology, University of Texas Medical Branch at Galveston, Galveston, Texas, USA
[2] Medical University of South Carolina, Charleston, South Carolina, USA,
[3] Division of Gastroenterology, Johns Hopkins Hospital, Baltimore, Maryland, USA
[4] Mayo College of Medicine, Rochester, Minnesota, USA

submitted 20 June 2007
accepted after revision 4 July 2007

Bibliography
DOI 10.1055/s-2007-966764
Endoscopy 2007; 39: 761–764 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
P. J. Pasricha, MD
Division of Gastroenterology
The University of Texas Medical Branch
4106 McCullough Building – Rt. 0764
Galveston 77555-0764
Texas
USA
Fax: +1-409-772-4789
jpasrich@utmb.edu

Background and study aims: The most permanent method of treating achalasia is a surgical myotomy. Because of the requirement for a mucosal incision and the risk of perforation, this procedure has not generally been approached endoscopically. We hypothesized that we could perform a safe and robust myotomy by working in the submucosal space, accessed from the esophageal lumen.

Materials and methods: Four pigs were used for this experiment. Baseline lower esophageal sphincter (LES) pressures were recorded and the pigs underwent upper endoscopy using a standard endoscope. A submucosal saline lift was created approximately 5 cm above the LES and a small nick was made in the mucosa in order to facilitate the introduction of a dilating balloon. After dilation, the scope was introduced over the balloon into the submucosal space and advanced toward the now visible fibers of the LES. The circular layer of muscle was then cleanly incised using an electrocautery knife in a distal–to–proximal fashion, without complications. The scope was then withdrawn back into the lumen and the mucosal defect was closed with endoscopically applied clips. The entire procedure took less than 15 minutes. Manometry was repeated on day 5 after the procedure and the animals were euthanized on day 7.

Results: LES pressures fell significantly from an average of 16.4 mm Hg to an average of 6.7 mm Hg after the myotomy. The necropsy examinations revealed no evidence of mediastinitis or peritonitis.

Conclusions: Endoscopic submucosal esophageal myotomy is feasible, safe, and effective in the short term. It has the potential for being useful in patients with achalasia. The submucosal space is a novel and potentially important field of operation for endoscopic procedures.

Introduction

Achalasia is a disorder affecting the esophagus that is characterized by a nonrelaxing lower esophageal sphincter (LES) with aperistalsis in the body of the esophagus. Although relatively uncommon, the disorder can cause significant morbidity, with dysphagia, regurgitaton, and weight loss. Therapy is palliative and is directed at lowering the LES pressure, with the aim of reducing the functional obstruction to bolus transit at this site. Current treatments include muscle relaxants (calcium-channel blockers, nitrates), endoscopic injection of botulinum toxin, pneumatic dilation, and surgical myotomy.

Myotomy is currently considered to be the most effective form of therapy for this condition, particularly in younger adults [1–4]. This operation is now most commonly performed via a laparoscopic route and this approach is associated with a significant improvement in both morbidity and immediate postoperative outcomes [5]. However, it is still an invasive procedure, requires general anesthesia, and is relatively expensive. In addition, patients whose operations fail (although this is uncommon) often subsequently require open surgery because of tissue adhesions in the region resulting from the previous operation [6,7]. Finally, there is a small but significant risk of damage to collateral structures such as the vagus nerve. There is therefore room for improvement in this procedure and we hypothesized that an effective myotomy could be achieved in a simpler manner, using an entirely endoscopic approach. We adopted a novel endoscopic approach, using a submucosal route to access the muscular layer directly, and we tested this in pigs. Our results suggest that endoscopic submucosal myotomy is simple and effective in the short term and is not associated with significant adverse effects.

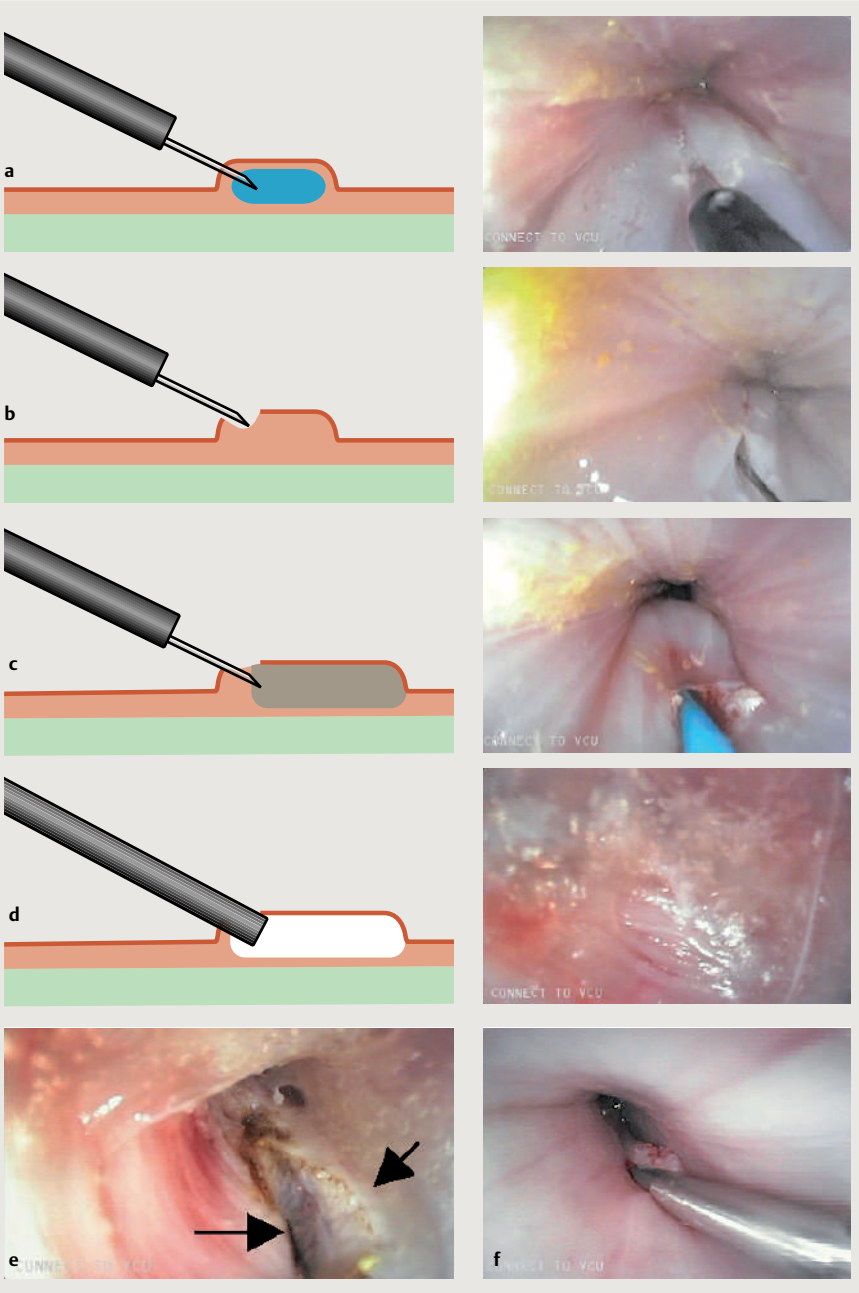

Fig. 1 The endoscopic myotomy procedure. **a** Normal saline was first injected into the submucosa. **b** An incision was made using an electrocautery knife to provide entry for the balloon catheter. **c** Balloon dilation was performed to accentuate the submucosal space. **d** The endoscope was then inserted into the submucosal space. **e** We then performed a myotomy of the circular muscle (the arrows point to the edges of the cut muscle). **f** The mucosal defect was finally closed with clips.

Materials and methods

Four young Yorkshire pigs (John Alber, Cibolo, Texas, USA) ranging in weight between 16 kg and 20 kg were used in this study. The study protocol was reviewed and approved by the University of Texas Medical Branch Institutional Animal Care and Use Committee.

Manometry

Baseline and postmyotomy LES pressures were recorded using a manometric catheter (internal diameter 1cm) with four side holes placed 5 cm apart and perfused with distilled water using a low-compliance pneumohydraulic system. Pressures within the catheter were transmitted to external transducers and recorded using an electronic interface (Polygraf; Synectics Medical Inc., Irving, Texas, USA).

Myotomy

After pre-anesthesia (using a mixture of xylazine, telazol, and ketamine), endotracheal intubation was carried out and the pigs were kept under general anesthesia using an isofluorane-oxygen mixture.

The pigs underwent upper endoscopy using a standard upper endoscope, 9 mm in diameter with a 2.8-mm working channel

Video 1

This is a composite video, put together for illustrative purposes only. It represents segments taken from several animals, using tools (needle-knives, balloons) that could be different from those described in the Materials and methods section of this paper.

online content including video sequences viewable at:
www.thieme-connect.de/ejournals/abstract/endoscopy/doi/10.1055/s-2007-966764

(EG-2770K; Pentax America Inc., Mountvale, New Jersey). Approximately 5 cm above the gastroesophageal junction, a submucosal injection with 0.9% normal saline was performed to lift the mucosa and expand the submucosal space to facilitate safe mucosal incision (**Fig. 1**, **Video 1**). A small nick was made in the mucosa using a unipolar needle-knife to facilitate the introduction of a controlled radial expansion (CRE) dilating balloon (10–11–12 mm; Boston Scientific, Natick, Massachussetts, USA). The scope was introduced over the balloon catheter and advanced distally into the submucosal space, where the circular muscle of the esophagus was seen below and the underside of the mucosa was seen above. The junction of the esophagus and the stomach was readily recognized by a change in the configuration of the muscular fibers from one of uniform circularity to a more irregular arrangement. At this point, using either an insulated-tip knife (Olympus, Tokyo, Japan) or a regular Boston Scientific needle-knife under direct visualization, the circular layer of muscle was cleanly incised in a distal–to–proximal fashion using a pure-cut current at a setting of 50 watts/second. The scope was then withdrawn back into the lumen and the mucosal defect was closed with endoscopically applied Boston Scientific Resolution Clips.

Postmyotomy period

The animals were given enrofloxacin (5 mg/kg) daily until the end of the study. Manometry was repeated 5 days after the procedure, and the animals were euthanized using pentobarbital on day 7 after the myotomy. Peritoneal, mediastinal, and thoracic examinations were performed postmortem, looking for signs of peritonitis or infection. The esophagus and proximal stomach were harvested and examined from the serosal and mucosal aspects.

Results

The procedure was successful in all the pigs. The average total procedure time for the endoscopy was 15 minutes (95% confidence interval 10–20 minutes). The first pig was sacrificed immediately because it had developed respiratory distress due to an unrelated cause. The other three pigs were observed for 1 week and appeared to do well, with no evidence of fever or loss of appetite.

The LES pressures fell significantly, from an average of 16.4 mm Hg at baseline to an average of 6.7 mm Hg after the myotomy ($P = 0.03$), representing a reduction of approximately 60% (**Fig. 2**). Necropsy revealed no evidence of mediastinitis or peritonitis. The esophageal mucosa had healed in all the pigs.

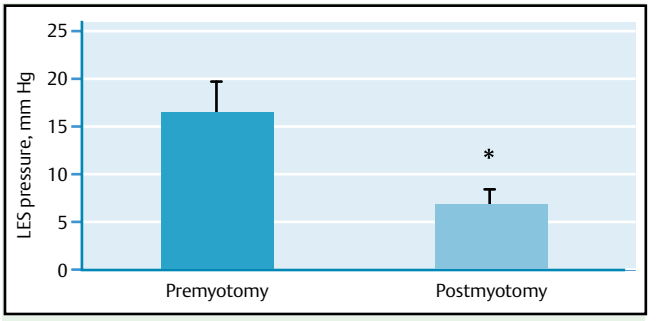

Fig. 2 The lower esophageal sphincter (LES) pressures in the experimental pigs (n = 3) before and after myotomy (premyotomy pressure vs. postmyotomy pressure, $P = 0.03$).

In most cases, the circular muscle layer appeared to be cleanly cut, with no significant adhesions or hemorrhage (**Fig. 3**).

Discussion

Endoscopic therapy and surgical therapy for achalasia both target the LES. The standard endoscopic approach in the treatment of achalasia consists of pneumatic dilation with large-diameter balloons, ostensibly to tear the LES muscle fibers. However, there has been no convincing experimental proof of dilation-induced disruption of the sphincter muscle [8]. This might explain why balloon dilation is generally not as effective as surgical myotomy in the palliation of symptoms and reduction of LES pressure. An endoscopic approach that is able to mimic the surgical myotomy procedure would therefore be of potential value.

To the best of our knowledge, there has been only one reported attempt at endoscopic myotomy of the LES, and this was published nearly three decades ago [9]. These investigators used an improvised needle-knife to cut the muscle from the luminal side in 17 patients and described what appeared to be excellent clinical, radiographic, and manometric results over a follow-up period ranging from 3 months to 25 months; bleeding occurred in three patients but this was easily controlled endoscopically. Despite these positive results, it should be pointed out that the major risk of the mucosal approach is that of mediastinal contamination from luminal contents, and the fear of this complication could also limit the depth of myotomy. This might be one reason why this study has apparently neither been repeated nor corroborated by others. Nevertheless, these results were intriguing and suggested that this technique might hold promise as an alternative to more invasive methods of myotomy.

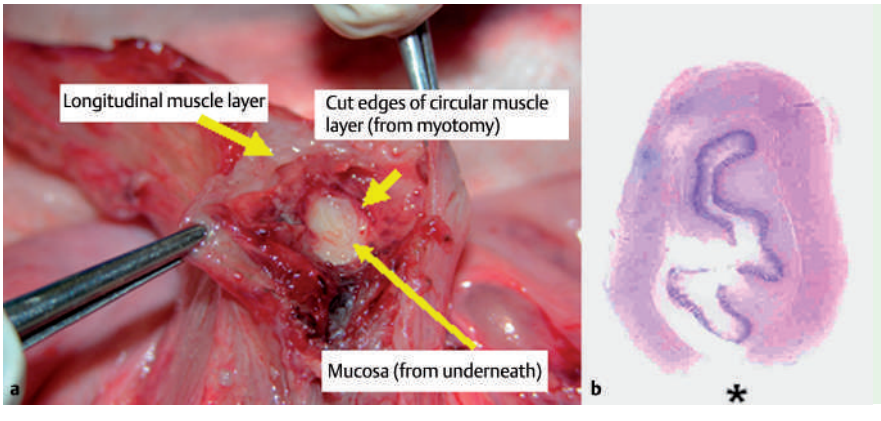

Fig. 3 The porcine esophagus at necropsy, showing the macroscopic view from the serosal side (**a**) and a histological view at the site of the myotomy, which is marked by the asterisk (**b**). Note the "neospace" in the adjacent submucosal area created by the scope in this view. (The break in the mucosa is an artifact of the sectioning procedure.)

In this study, using readily available endoscopic equipment, we attempted an improved method of endoscopic myotomy by directly approaching the muscular layer via a submucosal tunnel created by a balloon. This retains a mucosal flap that can then be tacked down with clips, thereby preserving the integrity of the mucosal lining and reducing the risk of mediastinal leakage of esophageal contents. This was attested to by the lack of ill-effects on postoperative animal behavior and the absence of overt mediastinitis or signs of infection at necropsy. Technically, our method was surprisingly easy and quick, requiring only an average of 15 minutes. The gastroesophageal junction is easily recognizable submucosally by the obvious change in the arrangement of muscle fibers and provides a reliable landmark for orientation.

Although these results are encouraging, our study has several limitations that need to be addressed before this technique can be enthusiastically endorsed for use in humans. The most important of these is the very short period of follow-up after the procedure. In contrast to the surgical procedure, the cut edges of the muscle are not kept physically apart and it is possible that, over time, partial or complete regrowth might occur, with accompanying recovery of LES tone. This is an area that might require technological innovation and we are currently working on novel versions of cutting devices in order to achieve a theoretically more robust myotomy. In addition, it is possible that multiple incisions at different sites could also be required for an optimal outcome. Furthermore, in these initial experiments we limited the myotomy to the esophageal side. Most surgeons believe that, to be effective, the myotomy has to be extended for up to 3 cm on the gastric side, in order to effectively eliminate resistance from the "clasp" fibers of the LES [10]. On the other hand, a highly effective endoscopic myotomy will leave the esophagus vulnerable to gastroesophageal acid reflux and its sequelae in much the same way as the surgical procedure does [11]. The surgical myotomy has the advantage of being able to provide a concomitant antireflux procedure, but it is recognized that it is not completely effective in preventing this complication [1]. Although one can envisage combining our technique with an endoscopic antireflux procedure, the results are likely to be even less robust than those of a surgical fundoplication. If our procedure was to be adopted and be successful in humans, therefore, patients might require chronic acid suppressive therapy. Finally, it should be pointed out that our technique has the theoretical advantage that it should be relatively simple to "redo" if required, unlike the surgical approach, where this can be complicated. As an aside, this technique reinforces the experimental support for the utility of a submucosal working space to gain access to the peritoneal or mediastinal cavities, as has been suggested by Sumiyama et al. [12]. This approach has the advantage of separating the breach in the muscular layer (i.e. an "offset" gastrotomy or esophagotomy) from that in the mucosa, with the result that closure of the mucosal breach alone might be sufficient to prevent leakage of luminal contents.

In conclusion, we have described a novel experimental submucosal approach for performing an endoscopic myotomy. This has potential for application in humans with conditions such as achalasia but could also theoretically replace surgical sphincterotomy and perhaps stricturoplasty at other sites. However, more work needs to be done on refining this technique, especially with respect to long-term safety and outcomes.

Acknowledgments

We would like to thank Dr. Doug Brining and his staff at the Animal Research Center at University of Texas Medical Branch for providing veterinary support.

Competing interests: This research was sponsored by Apollo Endosurgical Inc., Austin, Texas, USA. Drs. P. J. Pasricha, P. B. Cotton, C. J. Gostout, R. H. Hawes, S. V. Kantsevoy, and A. N. Kalloo are equity holders in this company.

References

1 *Hoogerwerf WA, Pasricha PJ.* Achalasia and other motor disorders. In: DiMarino AJ, Benjamin SB (eds). Gastrointestinal disease: an endoscopic approach. 2nd edn. Thorofare: Slack Inc, 2002: 299 – 330
2 *Spiess AE, Kahrilas PJ.* Treating achalasia: from whalebone to laparoscope. JAMA 1998; 280: 638
3 *Wong RKH, Maydonovitch CL.* Achalasia. In: Castell DO (ed). The esophagus. 2nd edn. Boston: Little, Brown and Co, 1995: 219
4 *Pehlivanov N, Pasricha PJ.* Achalasia: botox, dilatation or laparoscopic surgery in 2006. Neurogastroenterol Motil 2006; 18: 799 – 804
5 *Woltman TA, Pellegrini CA, Oelschlager BK.* Achalasia. Surg Clin N Am 2005; 85: 483 – 493
6 *Gorecki PJ, Hinder RA, Libbey JS et al.* Redo laparoscopic surgery for achalasia: is it feasible? Surg Endosc 2002; 16: 772 – 776
7 *Mercer CD, Hill LD.* Reoperation after failed esophagomyotomy for achalasia. Can J Surg 1986; 29: 177 – 180
8 *Vantrappen G, Jannsens J.* To dilate or operate? That is the question. Gut 1983; 24: 1013 – 1019
9 *Ortega JA, Madureri V, Perez L.* Endoscopic myotomy in the treatment of achalasia. Gastrointest Endosc 1980; 26: 8 – 10
10 *Oelschlager BK, Chang L, Pellegrini CA.* Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003; 138: 490 – 495
11 *Csendes A, Braghetto I, Burdiles P et al.* Very late results of esophagomyotomy for patients with achalasia: clinical, endoscopic, histologic, manometric, and acid reflux studies in 67 patients for a mean follow-up of 190 months. Ann Surg 2006; 243: 196 – 203
12 *Sumiyama K, Gostout CJ, Rajan E et al.* Transgastric cholecystectomy: transgastric accessibility to the gallbladder improved with the SEMF method and a novel multibending therapeutic endoscope. Gastrointest Endosc 2007; 65: 1028 – 1034