Universidade do Minho
Escola de Ciências da Saúde

João Moreira Pinto

Hybrid Thoracic NOTES: a translational research project

outubro de 2013

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Hybrid Thoracic NOTES: a translational research project

Tese de Doutoramento em Medicina

Trabalho realizado sob a orientação do
Professor Doutor Jorge Correia Pinto
e co-orientação da
Professora Doutora Carla Rolanda Gonçalves

outubro de 2013

«Consiste o progresso no regresso às origens: com a plena memória da viagem.»

Agostinho da Silva

Agradecimentos

À Professora Doutora Cecília Leão, Presidente da Escola de Ciências da Saúde (ECS) da Universidade do Minho, agradeço o privilégio de ser aluno desta escola. Agradeço a sua dedicação e incentivo à investigação de excelência que se faz nesta Escola e o seu trato afável com todos que nela trabalham.

Ao Professor Doutor Jorge Pedrosa, Director do Instituto de Ciências da Vida e da Saúde (ICVS) da ECS da Universidade do Minho, agradeço a possibilidade de investigar e de concretizar os projectos científicos a que me propus. Agradeço o facto de o ICVS existir e se preservar como uma instituição com meios físicos, técnicos e científicos de qualidade ímpar.

Ao Professor Doutor Jorge Correia-Pinto, meu Orientador deste percurso enquanto doutorando, Coordenador do Domínio de Investigação em Ciências Cirúrgicas do ICVS e, desde há uma ano, meu Director de Serviço no Hospital de Braga. É um exemplo de liderança. Um líder ampara na dificuldade, mas empurra-nos para a aventura e para o desafio quando assim tem de ser. Alimenta a criatividade e a vontade de chegar mais além. Um líder é um exemplo de perseverança e capacidade de trabalho. Agradeço esse exemplo. Agradeço a oportunidade de me ter integrado num grupo de investigação tão inovador, prestigiado nacional e internacionalmente, apetecido por qualquer médico interno, como eu era quando iniciei o desafio de me doutorar. Agradeço a oportunidade que me foi dada.

À Professora Doutora Carla Rolanda, Co-orientadora deste trabalho, a quem devo toda a formação em endoscopia flexível. Sem a sua perspectiva gastroenterológica, seria difícil imaginar e muito menos concretizar os procedimentos cirúrgicos que ensaiámos.

Ao Dr. José Alfredo Cidade Rodrigues, Director de Serviço de Cirurgia Pediátrica do Centro Hospitalar do Porto (à data do meu internato médico em Cirurgia Pediátrica), e ao Dr. Carlos Enes de Oliveira, meu Orientador de Formação. Ambos se empenharam na minha formação enquanto cirurgião pediátrico. Ambos me apoiaram na vontade de complementar essa formação com investigação laboratorial.

A todos os meus antigos colegas de serviço do Centro Hospitalar do Porto e aos meus actuais colegas de serviço do Hospital de Braga. Trabalhar nestas equipas foi e continua a ser uma fonte de aprendizagem imensa. Senti, como hoje continuo a sentir, compreensão dos colegas pelo facto de a investigação ocupar bastante tempo, e obrigar a uma certa flexibilização de horários.

Aos meus parceiros de investigação e para sempre amigos Alice Miranda e Aníbal Ferreira. Foram horas e horas a trabalharmos em conjunto para concretizarmos estas experiências. Muitos jantares adiados, muitos fim-de-semanas estragados. Passámos momentos de desespero juntos, mas também ultrapassámos todos os obstáculos e chegámos aqui juntos. Muito obrigado aos dois.

Aos meus colegas de docência, Ana Célia Caetano, Cristina Nogueira-Silva, Cristina Freitas, Emanuel Dias, Estevão Lima, Maria João Baptista, Paulo Mota, Rute Moura, Rui Duarte e Sara Hora Gomes. Pelo companheirismo e pela boa disposição.

Aos meus colegas de laboratório, Hélder Ferreira, Jaime Vilaça, Tiago Henriques-Coelho. Pela partilha de conhecimento e pelas vitórias sobre algumas dificuldades. Pela perspectiva de continuarmos a crescer juntos.

À minha família. Terão sido os mais prejudicados pela falta de tempo, pela indisponibilidade mental, pelo cansaço. Em nenhum momento deixaram de acreditar neste projecto e de me apoiar a concretizá-lo. Agradeço aos meus pais, pelo nascimento, pelo crescimento, pela educação. Agradeço aos meus avós pelo nascimento, pelo crescimento, pela educação das crianças que viriam a ser os meus pais. Agradeço ao meu irmão, Tiago, por vivermos juntos tudo o que vivemos (e é tanto). Agradeço aos meus filhos, João e Manuel, por serem a razão da minha vida.

À Michele, por ser a razão e a emoção da minha vida.

Abstract

Natural Orifice Transluminal Endoscopic Surgery (NOTES) is considered the next step on minimally invasive surgery. NOTES uses endoscopes entering through any single or combination of natural orifices - mouth, urethra, vagina, and anus, in order to perform surgery inside the thorax or the abdomen. Its main purpose is providing scarless and less painful surgery to patients. To perform NOTES in the thorax, gastroenterologists and surgeons have focused mainly on transesophageal access. Although the esophagus gives a direct access to the mediastinum and the pleural cavity, this hollow tube is in direct relation with important vital organs, namely heart, great vessels, vagus and phrenic nerves and all the respiratory tract. This makes an inside-out esophagotomy very risky. We suggested adding a single transthoracic port, in order to visualize and control the exact site of esophagotomy creation. We hypothesized that this hybrid approach would also be useful to tackle some of the hurdles of transesophageal endoscopic surgery. A single transthoracic port would permit the introduction of rigid instruments (for effective triangulation and counter-traction), insufflation of carbon dioxide (CO_2) and monitoring pneumothorax pressure. The aims of this PhD thesis were delineated to test the reliability of hybrid thoracic NOTES to perform thoracoscopic complex procedures. We carried out three experimental protocols in the porcine model with survival assessment - upper lobe pulmonary lobectomy, left atrial appendage (LAA) ligation, and thymectomy. In this last protocol we tested hybrid transesophageal access in the human cadaver. In all the experiments, transesophageal access was created under transthoracic thoracoscopic visual control without incidents. Instruments were inserted both through the esophagus and through the thoracic wall, permitting dissection, coagulation, ligation and suture, mimicking the two hands of a surgeon. All the procedures had pneumothorax pressure controlled by connecting a CO_2 insufflator tube to the transthoracic port. The site of transthoracic entry was useful for postoperative drainage. Taking all together, the results of our experiments prove that hybrid thoracic NOTES is reliable. Looking at the recent widespread of submucosal endoscopic dissection in esophageal procedures, in particular the per-oral endoscopic myotomy (POEM) for achalasia patients, we believe that translation of thoracic NOTES to humans might not take long. When time comes, we should keep in mind that hybrid

thoracic NOTES is the safest way to go.

Resumo

A Cirurgia Endoscópica Transluminal por Orifício Naturais, mais conhecida por NOTES (*Natural Orifice Transluminal Endoscopic Surgery*) é considerada o próximo passo evolutivo na cirurgia minimamente invasiva. O NOTES utiliza endoscópios introduzidos por um ou mais orifícios naturais – boca, uretra, vagina e ânus, de forma a permitir a execução de cirurgias dentro do tórax ou do abdómen. Os principais objectivos do NOTES são oferecer ao doente uma cirurgia sem cicatriz e menos dolorosa. No NOTES torácico, gastroenterologistas e cirurgiões têm se focado a sua atenção no acesso transesofágico. Embora o esófago permita um acesso directo à cavidade pleural e ao mediastino, este tubo oco está em relação directa com órgãos vitais, nomeadamente o coração, os grandes vasos, os nervos vagos e frénicos assim como a maior parte do trato respiratório. Isto faz da esofagotomia de dentro para fora, um procedimento arriscado. O nosso grupo sugeriu acrescentar ao acesso transesofágico um port único trans-torácico, de forma a conseguir-se um bom controlo visual do local da esofagotomia. Colocámos a hipótese de esta abordagem híbrida poder ser a solução de outros problemas do NOTES transesofágico. A introdução de um port trans-torácico permitiria a introdução de instrumentos rígidos (para uma triangulação e contra-tracção eficazes), a insuflação de dióxido de carbono e a monitorização da pressão do pneumotórax criado. Os objectivos desta tese foram desenhados para testar a eficácia e a segurança do NOTES torácico híbrido na execução de procedimentos toracoscópicos complexos. Foram realizados três protocolos experimentais no modelo do porco com sobrevida – lobectomia pulmonar superior esquerda, laqueação do apêndice auricular esquerdo e timectomia. Testámos também o acesso transesofágico híbrido no cadáver humano. Em todas as experiências, o acesso transesofágico foi criado sob contolo toracoscópico trans-torácico, sem incidentes. Os instrumentos de trabalho foram introduzidos pelo esófago e pela parede torácica permitindo dissecção, coagulação, laqueação e sutura, mimetizando as duas mãos de um cirurgião. Todos os procedimentos foram realizados sob pneumotórax controlado, ligando o insuflador de dióxido de carbono ao port trans-torácico. O local de entrada do port trans-torácico serviu para a colocação do dreno torácico no pós-operatório imediato. Resumindo, os resultados das nossas experiências provam que o NOTES torácico híbrido é seguro e

eficaz. Olhando para a recente aceitação e disseminação das técnicas de dissecção endoscópica submucosa para procedimentos no esófago, em particular a miotomia endoscópica para o tratamento da acalásia, acreditamos que a translacção do NOTES torácico poderá ser tentada num futuro muito próximo. Quando esse dia chegar, deveremos ter em mente que o NOTES torácico híbrido é a forma mais segura de o fazer.

Contents

Abreviations list

CCD - charged-couple device

CO_2 - carbon dioxide

ECC - endoscopic clip-closure

ECS – Escola de Ciências da Saúde

EMR - endoscopic mucosal resection

EUS – endo-ultrasonography

Hg - mercury

ICVS - Instituto de Investigação em Ciências da Vida e da Saúde

IM - intra-muscular

kg - kilogram

LE - lower esophagus

mm - millimeter

mg - milligram

NOTES - Natural Orifice Transluminal Endoscopic Surgery

O_2 - oxygen

OTSC - over-the-scope clip

POEM - per-oral endoscopic myotomy

SEMF - submucosal endoscopy with mucosal flap

UE - upper esophagus

Chapter I | INTRODUCTION

1. Introduction

1.1 A brief history of thoracoscopic surgery

Endoscopy seen as the inspection (*scope*) of the inside (*endo*) of the human body dates back to Hippocrates (460-375 B.C.). The Greek physician invented the first rectal *speculum*. The first simple gynecological *speculum* dates from about the same time (Lima, 2008). Yet, modern endoscopy is a nineteen century's invention. Philipp Bozzini, a German physician, was the first to develop a light source to achieve adequate endoscopic illumination. Bozzini combined reflexing mirrors, a candle, and an urethral cannula to direct light into the internal cavities. The device was called the *Lichtleiter*, which means light conductor (Bozzini, 1806). John D. Fisher (1798-1850) used the same physics principle to create an endoscope of his own, initially to inspect the vagina. Later, he modified it to examine the bladder and urethra (Picatoste *et al.*, 1980). In 1853, Jean Desormeaux, a French surgeon, considered by most the father of endoscopy, used a lamp of gasogen (a mixture of alcohol and turpentine) as the light source and introduced the use of lens to focus. This is considered the first widespread cystoscope, as he used it mainly for urological purposes. In 1869, Commander Pantaleoni modified it to cauterize a hemorrhagic uterine growth. Thus, Pantaleoni performed the first therapeutic hysteroscopy (Gunning and Rosenzweig, 1991). By the same time, in 1868, Kussmaul performed the first rigid gastroscopy in a patient who was a professional sword swallower (Walk, 1996).

In 1879, Thomas Edison invented the electrical light bulb. This huge step in mankind was rapidly used in favor of endoscopy. In 1886, both Maximilian Nitze from Germany and Josef Leiter from Vienna presented a cystoscope with a built-in light source formed from an electrically heated platinum wire, a multi-lens system, and a separate water circulation system for cooling. Later, Leiter together with Mikulicz built a rigid open-tube esophagoscope which would be adapted and used by ear, nose, throat and thoracic surgeons (Haubrich, 1987). The first semi-flexible gastroscope using a complex lens structure was presented in 1932 by Georg Wolf and Rudolph Schindler. In 1956, Hirschowitz presented the first flexible gastroduodenal endoscope using coherent fiber bundle. Finally, in 1983 the image was to be replaced by electronic video technology using a charged-couple device (CCD) chip, and the first flexible video-endoscope with working channel was presented (Classen and Phillip. 1984).

Doctors started using endoscopes to look through the abdominal and thoracic walls into the cavities of the human body very early. Cruise and Gordon were the first to introduce a cystoscope through a pleurocutaneous fistula of a child suffering from chronic empyema, in 1866. However, this was not followed by any further practical utilization (Tassi and Tschopp, 2010). During late 1910 and early 1911, Hans Jacobaeus, a Swedish internist, used the term ''laparothoracoscopy'' for the first time (Jacobeus, 1911). By 1912 he had performed closed-cavity endoscopy with a Nitze cystoscope in over 100 patients with ascitis and also described liver pathology, peritoneal tuberculosis, and tumors. He published his report on laparoscopy and thoracoscopy in humans in *Münchener Medizinische Wochenschrift*. A response by Kelling appeared two months later in the same journal, disputing Jacobaeus' claim to be the first to perform the procedure in humans, stating that he had successfully used celioscopy in two humans between 1901-1910 (Lima, 2008).

In 1915, Jacobeus described the lysis of pleural adhesions to create a pneumothorax as part of collapse therapy for tuberculosis. In cavitary pulmonary tuberculosis, he performed thoracoscopy under local anesthesia with two separate entry ports to allow electro-cauterization of adhesions under direct visual control. This was the beginning of thoracoscopic surgery. In the 1950s, the administration of antibiotic therapy for tuberculosis largely replaced the use of thoracoscopy in the treatment of this disease (Tassi and Tschopp, 2010). Thoracoscopic surgery would be restricted to biopsy procedures, management of pneumothorax, empyema irrigation, sympathetic chain ablation, and removal of intra-thoracic foreign bodies. The introduction of video imaging technology in the late 1980s and the wider availability of stapling devices facilitated an increasingly wider use of thoracoscopy for diagnostic and therapeutic procedures (Table I – Main achievements in history of thoracoscopic surgery). Beside better cosmesis, the advantage of VATS over thoracotomy lies in the reduction of both acute and chronic postoperative pain, permitting a faster recovery (Soica and Walker, 2000).

Table I. Main achievements in history of thoracoscopic surgery

1910	First thoracoscopic examination (Jacobeus)
1915	Lysis of pleural adhesions (Jacobeus)
1936	Thoracoscopy for diagnostic of spontaneous pneumothorax and pleural effusions (Sattler)
1942	First thoracoscopic sympathectomy (Hughes)
1950	Thoracoscopic ablation of blebs in the treatment of recurrent or persistent pneumothorax (Waterman)
1991	Thoracoscopic lung resection using endoscopic stapler (Krasna and Nazem)
1992	First thoracoscopic lobectomy (Lewis *et al.*)
1993	First Thoracoscopic esophagectomy (Gossot *et al.*)
1999	First thoracoscopic thymectomy (Tomulescu *et al.*)
2000	First thoracoscopic left atrial appendage ligation (Johnson *et al.*)
2000	First thoracoscopic repair of esophageal atresia with tracheo-esophageal fistula (Rothenberg SS)

1.2 Natural Orifice Transluminal Endoscopic Surgery

Natural Orifice Transluminal Endoscopic Surgery (NOTES) is the name given to endoscopic interventions on internal organs performed through natural orifices. Endoscopes enter the abdominal and thoracic cavities via any single or combination of natural orifices - mouth, urethra, vagina, and anus. NOTES dates back to 1940s, when Decker performed the first culdoscopies using an endoscope passed through the recto-uterine pouch to view pelvic organs and perform sterilization procedures (Decker, 1994). These procedures were superseded by non-invasive ultrasound imaging for diagnostic purposes and laparoscopy for surgical purposes. Later, NOTES was to be reborn when Rao and Reddy presented the video of the first transgastric appendectomy at the 2004 Annual

Conference of the Society of Gastrointestinal Endoscopy of India (Reddy and Rao, 2004). In a severely burnt patient, whose skin they could not incise, they used a therapeutic flexible gastroscope to reach his stomach. Then, they performed an inside-out gastrostomy and pushed the gastroscope through the gastric wall into the abdominal cavity. They looked for the appendix and performed the first ever transgastric appendectomy.

The first description of transgastric peritoneoscopy published in paper was by Kallo *et al.* in 2004. The authors used the porcine model (Kallo *et al.*, 2004). Soon, other natural orifices were presented as good access points for NOTES. Pai *et al.* published transcolonic peritoneoscopy followed by a series of transcolonic procedures (Pai *et al.*, 2006). The access from below permitted a good, direct view of the upper abdominal cavity. Having this in mind, Lima *et al.* presented transvesical endoscopic peritoneoscopy (Lima *et al*, 2006). To accomplish NOTES procedures in the thorax and the mediastinum, Sumiyama *et al.* proposed transesophageal access (Sumiyama *et al.*, 2007). Transvesical-transdiaphragmatic, transgastric-transdiaphragmatic and transtracheal access have been suggested too (Lima *et al.*, 2007; De Paloma *et al.*, 2010; Liu *et al.*, 2010). Anyway transesophageal has been preferred as a direct entry to the thorax and has permitted several procedures in porcine model, namely mediastinoscopy, thoracoscopy, lymphadenectomy, pleural biopsy, myocardial and left atrium injection, pericardial fenestration , epicardial ablation, cardiomyotomy, esophagomyotomy, vagotomy and sympathectomy (Fritscher-Ravens *et al.*, 2007; Willingham *et* al., 2008; Sumyiama *et al.*, 2008; Gee *et* al., 2008; Woodward *et* al., 2008; Fritscher-Raves, 2009; Turner *et al.*, 2010).

The main goal of NOTES is to avoid skin incisions and its associated complications, such as wound infections and hernias. Theoretical advantages of NOTES include reduction in hospital stay, faster return to bowel function, decreased post-operative pain, reduction/elimination of general anesthesia, performance of procedures in an outpatient or even office setting, possibly cost reduction, improved cosmetic outcomes, and increased overall patient satisfaction.

NOTES has been even proposed as an alternative in patients where laparoscopy or conventional laparotomy is not desirable or contra-indicated. In this sequence, extremely obese patients might benefit from procedures that avoid skin incision and subcutaneous adipose tissue manipulation, preventing local infection. The same applies to patients with severe abdominal wall scars, infection or burn lesions. Furthermore, patients in Intensive Care Units may benefit from bedside procedures using portable endoscopes instead of being transported to the operating room. Finally, as with other endoscopic procedures, NOTES does not require general anesthesia with endotracheal intubation. So, it may be an option in patients who cannot be submitted to one.

In 2010, at the beginning of our experiments, we wrote a review on NOTES. In that article we went through history of NOTES in more detail, compiled the animal and human experience until that date, questioned what were the hurdles at that time and thought of the developments that could take place in the future. It was a good head start for this thesis (Annex 1).

1.3 Hybrid Thoracic NOTES

As stated before, esophagotomy has been preferred as a direct entry to the thorax for NOTES procedures. Until 2010, transesophageal NOTES had permitted several procedures in porcine model, but all of them were very low complexity procedures. Flexible endoscopic instruments entering through one or two working channels of the gastroscope lack the strength and the triangulation that are necessary for wide dissection, tissue manipulation, suture and anastomosis establishment. Without these, thoracic NOTES would not able to move on to more complex procedures. Moreover, the variety of instruments that can go through the working channels of flexible gastroscopes is very limited.

But the major hurdle for transesophageal access is the fact that performing an inside-out esophagotomy is highly risky because of possible mechanical abrasion and trauma of surrounding structures (Sumyiama *et al.*, 2008; Von Rentein *et al.*, 2011). Fritscher-Ravens *et al.* proposed endo-ultrasonographically (EUS)-assisted transesophageal access. In a comparative study of NOTES alone against EUS-assisted NOTES procedures, the authors found that the last was superior in gaining access, identifying structures, and therefore avoiding major complications (Fritscher-Ravens *et al.*, 2008). But this method could not avoid every complications.

A different alternative was presented by Rolanda *et al.*: single transthoracic port assistance for transesophageal NOTES (Rolanda *et al.*, 2008). As most thoracic procedures imply some time of postoperative tube drainage, a 12 mm incision was made in the thoracic wall and a 10 mm port was inserted before esophagotomy was performed. Using a 10 mm thoracoscope with a 5mm working channel (Karl Storz, Tuttlingen, Germany) inserted through the transthoracic port, transesophageal port was safely created with thoracoscopic visual control. Besides safe esophagotomy creation, the single transthoracic assistance permitted triangulation, counter-traction and the introduction of a wide variety of rigid instruments. Therefore, transeophageal NOTES was now able to move forward towards more complex thoracic procedures.

This was the starting point for this thesis. We believed that transesophageal NOTES with the assistance of a single transthoracic port, also known as hybrid thoracic NOTES, was the key to perform high complexity thoracoscopic procedures as well as give a safe start for human translation.

1.4 Aims

We proposed several animal studies with survival assessment and one experiment in the human cadaver to confirm the safety and reliability of hybrid thoracic NOTES. We tested three highly complex thoracic procedures. The following specific aims were pursued in this thesis:

1. To carry out pulmonary lobectomy by hybrid thoracic NOTES (survival assessment in the porcine model);
2. To carry out left atrial appendage (LAA) ligation by hybrid thoracic NOTES (survival assessment in the porcine model);
3. To carry out thymectomy by hybrid thoracic NOTES (survival assessment in the porcine model and human cadaver);

Chapter 2 | HYBRID THORACIC NOTES

PULMONARY LOBECTOMY

2. Hybrid thoracic NOTES pulmonary lobectomy

Moreira-Pinto J, Ferreira A, Miranda A, Rolanda C, Correia-Pinto J. Transesophageal pulmonary lobectomy with single transthoracic port assistance: study with survival assessment in a porcine model. Endoscopy 2012; 44: 354-361.

Transesophageal pulmonary lobectomy with single transthoracic port assistance: study with survival assessment in a porcine model

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submitted 12. July 2011
accepted after revision 15. November 2011

Bibliography
DOI http://dx.doi.org/10.1055/s-0031-1291594
Endoscopy 2012; 44: 354–361

ISSN 0013-726X

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Background and study aims: Thoracoscopic pulmonary lobectomy is being performed in an increasing number of patients. The aims of the current study were to assess natural orifice transluminal endoscopic surgery (NOTES) as an alternative to transthoracic endoscopic surgery, and to test the feasibility of peroral transesophageal right upper pulmonary lobectomy with the assistance of a single transthoracic trocar.
Methods: In 10 acute and 4 survival pigs, right upper pulmonary lobectomy was performed using a forward-viewing double-channel gastroscope and an operative thoracoscope with a 5-mm working channel inserted through a single transthoracic 12 – mm) port. Time, safety, and feasibility of the following steps were recorded in all animals: esophagotomy, hilar dissection, individual ligation of the hilum elements, pulmonary lobectomy, and specimen retrieval. In the survival experiments, esophagotomy was closed using a reticulated laparoscopy suture device and an esophageal stent was placed. These animals were kept alive and monitored for 2 weeks.
Results: Esophagotomy was performed safely in all animals (mean procedure duration 5.4 ± 1.7 minutes). Dissection of the right upper lobe hilum elements (bronchus, arteries, and veins) was carried out without adverse events. Individual ligation of the hilum elements was performed in all but two cases (time for dissection and ligation 44.2 ± 14.8 minutes). Lobectomy and specimen retrieval were completed in all animals (9.5 ± 3.1 minutes). Esophagotomy closure and stent placement were carried out in 20.0 ± 2.8 minutes in the survival animals. These animals fed normally and gained weight postoperatively without signs of disease. Endoscopic examination before necropsy revealed a pseudo-diverticulum in one animal, and wound dehiscence with confined collection/recess in the remaining animals.
Conclusions: Transesophageal right upper pulmonary lobectomy using single transthoracic trocar assistance is feasible and may represent a step towards scar-free pulmonary lobectomy.

Introduction

In natural orifice transluminal endoscopic surgery (NOTES), new approaches to the thorax are emerging as alternatives to the classic transthoracic endoscopic surgery. In 2007, Sumiyama et al. proposed transesophageal access to the thoracic cavity [1]. Since then, transvesical – transdiaphragmatic thoracoscopy [2], transgastric – transdiaphragmatic thoracoscopy [3], and transtracheal thoracoscopy [4] have also been suggested. The transesophageal approach has been considered preferable as a direct entry to the thorax and posterior mediastinum for several simple thoracic procedures in porcine models [5 – 11]. However, the transesophageal approach is typically considered to be highly risky because of possible mechanical abrasion and trauma sustained by surrounding structures. Moreover, an ineffective esophagotomy closure can be devastating, resulting in serious infectious complications. In fact, some of the recognized difficulties of NOTES procedures, such as safe port creation, infection prevention, tissue manipulation, and suturing and anastomosis establishment, seem to be particularly relevant in the transesophageal approach. In view of this, Rolanda et al. recently proposed the combination of single transthoracic trocar assistance with transesophageal NOTES in order to increase the safety and feasibility of more complex procedures [12].

Video-assisted thoracoscopic surgery (VATS) was first described in the early 1990 s. Initial applications included chest exploration, pleural effusion or pneumothorax management, and limited resection of lung nodules [13 – 16]. As minimally in-

vasive techniques improved, clinical application of VATS became progressively widespread for more complex procedures. Through this technique, VATS lobectomy became feasible and safe even for oncologic resection [17 – 22]. The endoscopic approach allows meticulous hemostasis, decreased pain, diminished inflammatory response, preserved postoperative pulmonary function, and more rapid return to preoperative activity [23].
We hypothesized that pulmonary lobectomy might be an indication for thoracic NOTES in the future. Therefore, a research protocol was designed to assess the feasibility of peroral transesophageal pulmonary lobectomy using the assistance of a single transthoracic trocar.

Material and methods

Study design

A total of 14 female pigs (*Sus scrofus domesticus*) weighing 35 – 45 kg underwent a complex thoracic procedure by hybrid NOTES – transesophageal right upper pulmonary lobectomy using the assistance of a single transthoracic trocar. After an initial learning curve, where four animals were used to test all steps in the procedure, using different approaches, different scopes, different instruments, and different techniques (results are not reported here), 14 consecutive in vivo experiments were carried out – 10 animals in the acute study and 4 animals in a survival assessment. All surgical endoscopic and thoracoscopic procedures were recorded. Vital and physiological parameters of well-being were monitored during the experiment. The time of the procedure was recorded, as well as the difficulties and complications encountered at each step of the procedure. The animals in the survival group were monitored for 15 days. Endoscopic examination and necropsy were undertaken in all animals at the end of the protocol (after the procedure in the acute animals and after 15 days in the survival animals). The study was approved by the ethical review boards of Minho University (Braga, Portugal).

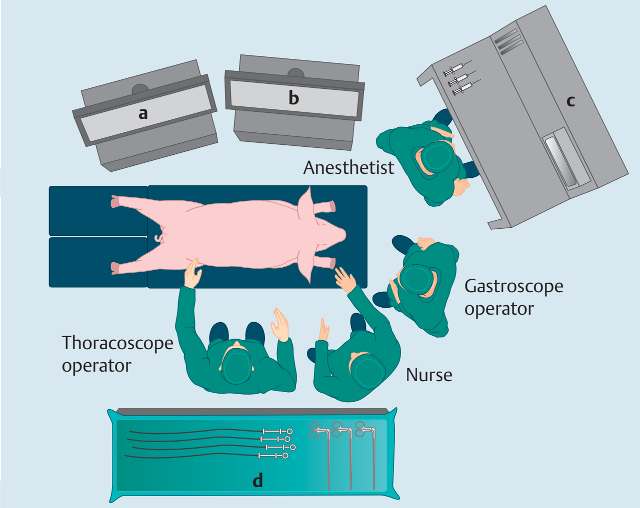

Fig. 1 Room ergonomics. **a** Thoracoscope monitor. **b** Gastroscope monitor. **c** Ventilator. **d** Back table for equipment.

Pig preparation

All procedures were performed under general anesthesia with endotracheal intubation and mechanical ventilation (**Fig. 1**). Pigs were fasted for 8 hours and water was withheld for 4 hours before surgery. Pigs were premedicated with a combination of azaperone (4 mg/kg, intramuscularly [IM]), midazolam (1 mg/kg, IM), and atropine (0.05 mg/kg, IM). Anesthesia was induced with propofol (6 mg/kg, intravenously [IV]), and maintained with continuous propofol infusion (20 mg/kg/hour, IV) and buprenorphine (0.05 mg/kg, IM).

Surgical technique

The main steps of the procedure described herein are schematically illustrated and can be followed in **Fig. 2**. The pig was placed in the prone position (Cuschieri position). A 12-mm trocar (Excel port; Ethicon Endo-Surgery, Cincinnati, Ohio, USA) was inserted on the eighth intercostal space in the right posterior axil-

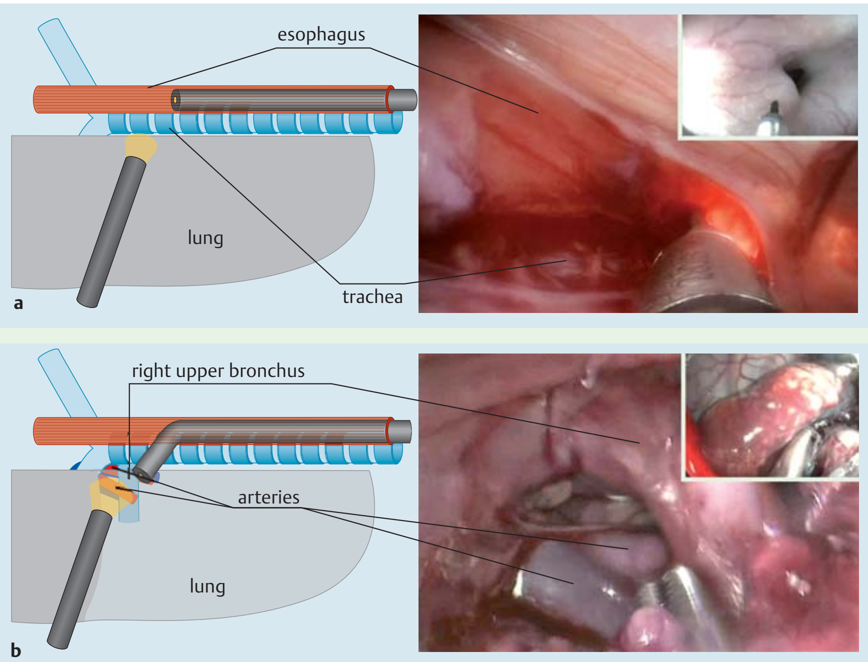

Fig. 2 Steps for transesophageal pulmonary lobectomy. Main image represents thoracoscopic view. Small upper right image represents gastroscopic view. **a** After introducing the gastroscope into the esophagus, a 1-cm transverse esophagotomy was carried out in the upper third using an endoscopic submucosal dissection knife under thoracoscope image control. **b** Anatomic dissection of the right upper hilum was performed using flexible (gastroscope) and rigid (thoracoscope) instruments.

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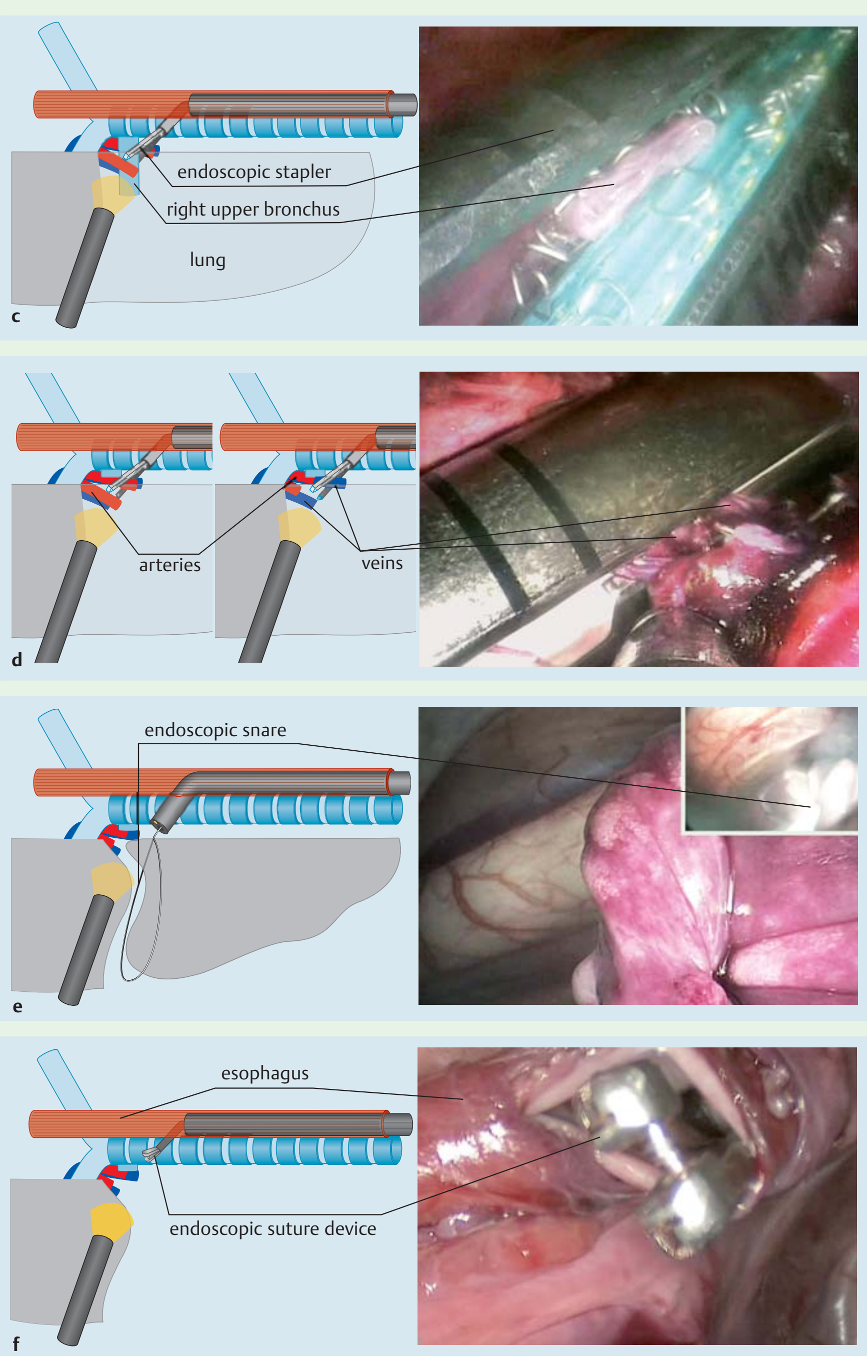

c After individual dissection, the bronchus was stapled using a 45-mm long, linear endostapler introduced through the oro-esophageal overtube.

d Independent right upper pulmonary arteries and veins were ligated using a 45-mm long, linear endostapler introduced through the oro-esophageal overtube.

e After completing the lobe resection using an endoscopic snare with cautery, the specimen was extracted retrogradely through the mouth.

f The esophagotomy was stitched and tied using SILS Stitch and a long knot-pusher, both handled through the oro-esophageal overtube.

Fig. 2 continued

lary line. CO_2 was insufflated through this transthoracic trocar. Pressure was maintained up to 6 mmHg. An operative thoracoscope with a 5-mm working channel (Straight Forward Telescope 0º 26034AA; Karl Storz GmbH, Tuttlingen, Germany) was introduced through the trocar.
A forward-viewing double-channel gastroscope (G28/34, Karl Storz) was inserted throughout an oropharyngeal overtube (US Endoscopy, Mentor, Ohio, USA) into the esophagus (**Fig. 2 a**). A 1-cm transverse esophagotomy was carried out in the upper third of the esophagus using a needle-knife (KD-11Q-1; Olympus, Tokyo, Japan) introduced through the gastroscope working channel. All transesophageal procedures were carried out under gastroscopic and thoracoscopic image control.
Anatomic dissection of the right upper hilum was performed using both flexible instruments (grasper 11252MX, electrocoagulation grasper 13773H; Karl Storz) and rigid devices (43-cm long, 5-mm Kelly dissector 33410ML, and scissors 34410MW; Karl Storz), which were introduced through the working channels of the gastroscope or the thoracoscope, respectively (**Fig. 2 b**). The dissection of the pulmonary hilum was carried out from posterior to anterior. Thus, after individual dissection and isolation of the right upper bronchus and associated pulmonary arteries and veins, a long linear endostapler with distal 45º degrees of articulation freedom (EndoPath; Ethicon Endo-Surgery) was inserted through the oro-esophageal overtube. Using 45-mm load staplers, the hilum elements of the right upper lobe were divided and individually ligated with thick tissue (green) load staplers for the bronchus (**Fig. 2 c**) and with vascular (white) load staplers for arteries and veins (**Fig. 2 d**). After the division of the airway and vascular elements of the right upper lobe hilum, resection was completed by separating and grasping the remaining lung parenchyma through the pulmonary fissure (which is incomplete

in pig model) using a flexible endoscopic snare (110220 – 01; Karl Storz) with cautery (▶ **Fig. 2 e**). Once released, the resected lobe was caught by the same gastroscopic snare, and the specimen was extracted retrogradely through the esophagus and mouth under image monitoring from the operative thoracoscope. After resection, the pulmonary surface was tested for air leakage under saline and high volume ventilation.

In the survival group, in addition to the surgical procedure described above, the esophagotomy was closed using one full-thickness 3 – 0 polyglactin stitch performed with a reticulated laparoscopy suture device (SILS stitch; Covidien, Mansfield, Massachusetts, USA) and a 5-mm knot-pusher, both introduced perorally through an overtube (US Endoscopy) and manipulated under thoracoscope image control (▶ **Fig. 2 f**). Afterwards, a covered 80-mm long esophageal stent with 20-mm diameter (Hanarostent NES-00 – 080 – 070 fully covered; MITech, Seoul, Korea) was placed using a guide wire inserted through the gastroscope. Both endoscopic and thoracoscopic visual assistance were used to position the upper limit of the esophageal stent 5 cm above the esophagotomy. Saline was injected through the gastroscope and signs of leakage were checked using thoracoscopic visualization. At the end of the procedure, the pneumothorax was drained using a thoracic tube introduced through the transthoracic trocar. No tube was left in place. The trocar skin incision was sutured using non-absorbable independent stitches.

Postoperative care (survival group)

At the end of the surgical intervention, all animals received a single dose of buprenorphine (0.05 mg/kg, IM) and meloxicam (0.4 mg/kg, IM). Antibiotic ceftiofur hydrochloride (5 mg/kg, IM) was repeated at 24-hour intervals for three consecutive days. A regular diet was resumed 8 hours after surgery. The animals were closely monitored for any signs of postoperative complications, distress, behavioral changes, anorexia, or weight loss.

After the follow-up period, the animals were anesthetized for endoscopic examination and esophageal stent removal. Necropsy was then performed to check the healing of the esophagus wall incision and for signs of pulmonary complications.

Results

The overall results of the study are summarized in ▶ **Table 1**. The prone approach and CO_2 insufflation facilitated good exposure of the intrathoracic esophagus without the need for additional retraction instruments or any kind of selective ventilation. Esophagotomy was performed safely in all animals without incident (▶ **Fig. 2 a**; ▶ **Video 1**). The mean duration of esophagotomy was 5.4 ± 1.7 min.

Dissection of the right upper lobe hilum elements (bronchus, arteries, and veins) was carried out in all animals without significant problems (▶ **Fig. 2 b**; ▶ **Video 2**). Pigs have an upper right bronchus emerging directly from the trachea, and the vessels (two arteries and two veins) in relation to this bronchus derive from the main pulmonary trunk vessels. Most of the dissection was done using a rigid dissector inserted through the working channel of the thoracoscope. Flexible gastroscope instruments were essential for counter-traction and for enhancing exposure of major vessels. By introducing instruments through both the mouth and the thoracoscope, triangulation was very similar to that experienced using an exclusive thoracoscopic approach. When small vessels were disrupted, the flexible gastroscope allowed prompt suction, clear identification of hemorrhagic origin, and hemostasis using a flexible coagulation grasper introduced through its working channel. Moreover, the flexible gastroscope was particularly useful in showing some parts of the thoracic cavity that could not be visualized with the 0º optic of the operative thoracoscope, namely lateral thoracic wall, diaphragm, and the anterior aspect of the hilum. The combination of the two endoscopic images resulted in a safer procedure.

Oro-esophageal handling of the endoscopic staplers for individual ligation of the hilum elements under transthoracic imaging was surprisingly feasible, reasonably easy to perform, and reliable in 11 cases. By stapling the bronchus first, it was possible to collapse the lobe before all of the vessels had been dissected. Therefore, after cutting the bronchus the lobe fell anteriorly, further exposing these vessels. In two cases, the ligation of the upper vessels (vein and artery) was en bloc. In one case, severe hemorrhage occurred due to incomplete vein ligation. However, even in this case, it was possible to control bleeding by grasping the hemorrhagic point with the gastroscopic grasper and using electrocoagulation alone through the dissector, which was introduced transthoracically. The mean time for hilum dissection and ligation of its elements was 44.2 ± 14.8 min (▶ **Fig. 2 c, d**, ▶ **Video 3** and ▶ **Video 4**).

After functionally excluding the right upper lobe it was easy to find the plane for lobe section once it lost ventilation and its color was changed. By inserting a grasper through the transthoracic scope, the lobe was pulled into the gastroscope flexible snare. Lobe transection was performed using cautery in all experi-

Video 1

Esophagotomy. Main image represents gastroscopic view, and small right upper image represents thoracoscopic view. The gastroscope is inserted into the esophagus. With thoracoscopic assistance one can determine the exact site for esophagotomy. A 1-cm transverse esophagotomy is performed using an endoscopic submucosal dissection knife under thoracoscope image control.

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Video 2

Hilum dissection. Main image represents gastroscopic view, and small upper right image represents thoracoscopic view for 20 s (beyond 20 s only the thoracoscopic view is shown). Anatomic dissection of the right upper hilum was performed using flexible (gastroscope) and rigid (thoracoscope) instruments.

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www.thieme-connect.de/ejournals/abstract/endoscopy/doi/10.1055/s-0031-1291594

Video 3

Bronchus ligation. Main image represents thoracoscopic view. The right upper bronchus is stapled using a 45-mm long, linear endostapler inserted through the oro-esophageal overtube.

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Table 1 Results of 10 acute and 4 survival experiments.

Case	Procedure duration, minutes			
	Esophagotomy	**Dissection and ligation of hilum elements (complications)**	**Lobe transection and specimen retrieval (complications)**	**Esophagotomy closure (complications)**
Acute study				**N/A**
1[1]	6	60	5	N/A
2	3	60	8	N/A
3	6	54 (Small parenchymal hemorrhage controlled without the need for coagulation)	13	N/A
4	6	57	9	N/A
5	5	76	12	N/A
6	6	44	10	N/A
7	8	36 (En bloc ligation of the upper vein and artery)	14	N/A
8	7	32	5	N/A
9	4	34 (Severe hemorrhage from incomplete vein ligation, controlled with coagulation alone)	12	N/A
10	6	30 (En bloc ligation of the upper vein and artery)	7	N/A
Survival study[2]				
11	3	38	5	20
12	3	38	12	24
13	5	36	9	18
14	8	24	12 (Small bronchial artery hemorrhage controlled with electrocoagulation alone; small parenchymal hemorrhage of the remaining lobe controlled with electrocoagulation alone)	18

[1] Died from cardiac arrest at 71 min.
[2] Survived for 15 days.

ments. In two cases, non-oxygenated tissue was left in place. Consequently, a second resection had to be performed. The same snare was used to retrieve the specimens through the esophagus, into the mouth. Pulmonary tissue collapsed easily permitting it to squeeze through the esophagotomy (**Fig. 2e**, **Video 5**). The mean time for lobe transection and specimen retrieval was 9.5 ± 3.1 min.

One animal in the acute group died before pulmonary lobectomy was completed, due to cardiac failure. All other animals were kept alive until the end of the acute experiment, at which point they were sacrificed.

In the survival group, esophagotomy closure was achieved with one or two stitches that could reasonably approximate the margins of the esophagotomy. In order to use the SILS stitch (Covidien) one has to take the gastroscope out. All of the movements of this suture device were guided by the image on the thoracoscope. The simultaneous insertion of the grasper through the working channel of the thoracoscope aided the positioning of the esophagus wall margin within the jaws of the suture device. In this way, it was possible to achieve a full-thickness wall suture of the esophagus in all experiments. Moreover, the grasper permitted the stitch to be pulled to the inside of the thorax so that the suture device could move freely without tension (**Fig. 2f**, **Video 6**). After the esophageal stent was left in place, no leak-

Video 4

Ligation of arteries and veins. Main image represents thoracoscopic view. The arteries and the veins going to right upper bronchus are stapled using a 45-mm long, linear endostapler (introduced) through the oro-esophageal overtube.

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Video 5

Lobe transection and specimen retrieval. Main image represents gastroscopic view, and small right upper image represents thoracoscopic view. The right upper pulmonary lobe is resected using an endoscopic snare with cautery. The specimen is extracted retrogradely through the mouth.

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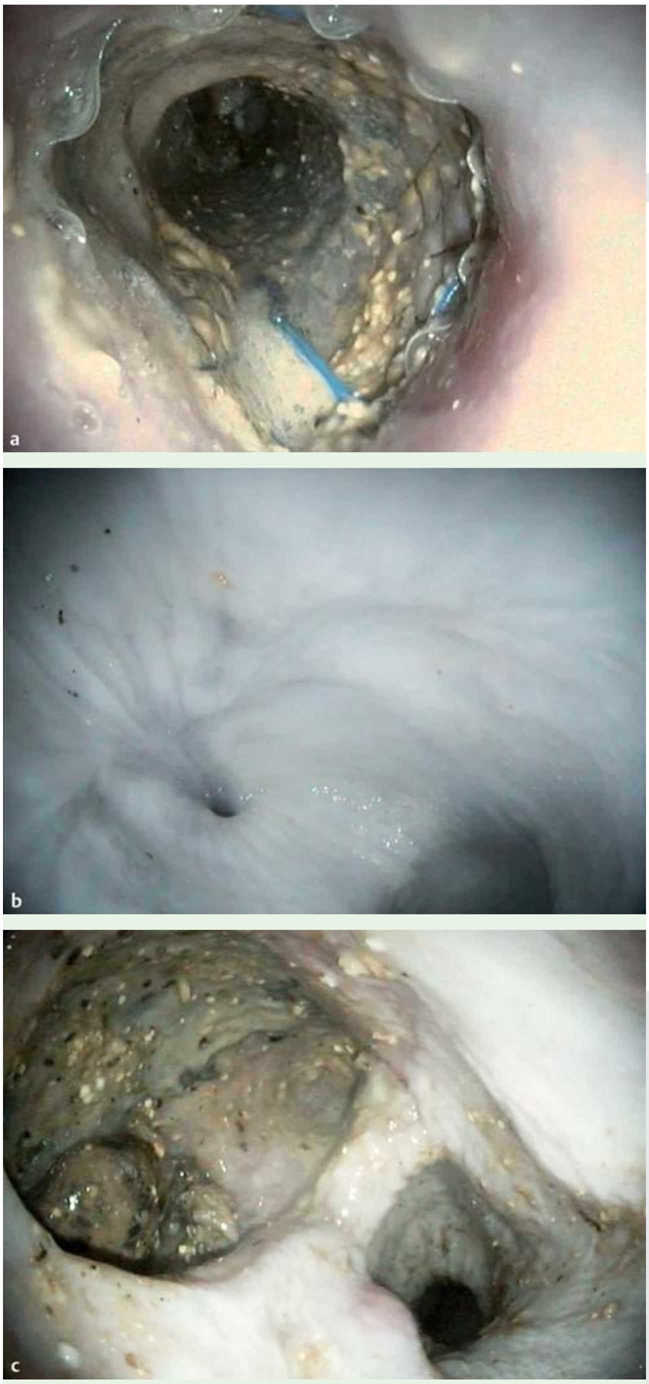

Fig. 3 Esophagotomy closure. **a** Esophageal stent in place on postoperative day 15. **b** Pseudo-diverticulum after esophageal stent removal on postoperative day 15. **c** Necrotic recess after esophageal stent removal on postoperative day 15.

Video 6

Esophagotomy closure. Initially only thoracoscopic view is shown. Beyond 1 min and 12 s, the main image represents the gastroscopic view and small right upper image represents thoracoscopic view. The esophagotomy is stitched and tied using SILS Stitch and a long knot-pusher, which are handled through the oro-esophageal overtube. Then, the esophageal stent is left in place.

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age was found. The mean time for esophagotomy closure and stent placement was 20.0 ± 2.8 min. The total mean operative time in the survival group was 68.7 ± 6.4 min.

All four animals in the survival group survived for 15 days. After recovery of anesthesia, the pigs tolerated a regular diet starting 8 hours after surgery, and they ambulated freely and displayed normal behavior. No adverse event occurred during the survival period. Endoscopic examination before necropsy revealed a pseudo-diverticulum in one animal (▶ **Fig. 3 a, b**), and wound dehiscence with confined collection/recess in the remaining three animals. These findings suggest incomplete healing of the esophagotomy. The esophageal necrotic recess did not communicate with the thorax or the pericardium (▶ **Fig. 3 c**). No stent migration was observed. No esophageal strictures were found. Postmortem examination revealed pleural adhesions on the site of pulmonary lobectomy. There were no signs of infection in the ipsilateral or counter-lateral lung parenchyma.

Discussion

VATS is becoming the gold standard for pulmonary lobectomy for both benign and oncologic diseases [18 – 23]. In NOTES, video-assisted thoracoscopy may be performed by a transesophageal approach, thereby avoiding intercostal neuralgia and reducing postoperative pain for the patient [6]. In porcine models, the transesophageal approach permitted mediastinoscopy and thoracoscopy, lung and pleura biopsy, lymphadenectomy, pericardial fenestration, vagotomy and esophagomyotomy, Heller myotomy, esophageal wall resection, and sympathectomy [1, 5 – 11]. More recently, Rolanda et al. established the concept of hybrid thoracic NOTES. By introducing a transthoracic trocar, the authors overcame some potential risks of the transesophageal approach, namely blind esophagotomy creation, esophagotomy closure, and thoracic drainage at the end of the procedure. Furthermore, triangulating instruments inserted through the flexible gastroscope and the transthoracic working channel, and the images provided by both scopes permitted a complex intra-thoracic procedure to be performed – segmental esophagectomy with esophago-esophageal anastomosis [12].

As discussed earlier, the prone position allows gravity to provide good esophageal exposure with minimal handling. It was not necessary to retract the lung and therefore the transthoracic instruments could be focused on the complex surgical procedure. The thoracic trocar was very useful for CO_2 insufflation and also for pressure control. It also permitted control of the esophagotomy, which was performed from inside to outside of the esophagus; by locating the exact position (side and level) for esophagotomoy creation, the thoracic trocar assisted the gastroscope in achieving the best approach to the pulmonary hilum. Furthermore, when the procedure was completed, the trocar site was used for tube insertion and acute pleural drainage. This port might be important in the human setting, as such a procedure would not be attempted without at least 24 hours of thoracic drainage.

Combining two opposite sites, for the entrance of scopes and respective instruments, regular triangulation and counter-traction could be achieved, which simulate the two hand movements of the surgeon, promoting secure manipulation of tissues, careful dissection of the pulmonary hilum, and effective electrocoagulation for hemorrhagic control. As mentioned earlier, the flexible endoscope inside the thorax makes it possible to examine the whole cavity including sites where rigid transthoracic endoscopes cannot reach – namely the chest wall. It should be emphasized that flexible instruments were used and the gastroscope was introduced through the mouth but rigid instruments such as the staplers, the SILS stitch, and the knot-pusher were also used. In fact, the use of an oro-esophageal overtube permitted the rapid access of all of these instruments into the thoracic cavity. Coordinating the movement of a rigid instrument through the mouth with the image provided by the thoracoscope is what made the ligation of the right upper bronchus and its vessels possible and reliable. Moreover, the rigid dissector inserted through the operative thoracoscope made positioning easier and faster.

As the same endoscopic stapler was used throughout the first nine experiments, it is possible that failure to completely ligate the pulmonary veins was due to ineffective stapling related to detrition of equipment. A new stapler was used after this event, and no further failures occurred.

Various solutions for endoscopic esophagotomy closure have been suggested. Creation of a submucosal tunnel that will not require mucosal suture has been used the most [1, 7], but it would not permit the retrieval of large specimens. The self-approximating transluminal access technique that has been used successfully in transgastric procedures even with specimen retrieval [24] would not work in this case, because during pulmonary lobe retrieval esophageal mucosa is easily disrupted. Endoscopic clips, suturing systems prototypes [6], esophageal stents [25], T-tags [26], and Padlock G clips [27] have also been suggested, but none of them seems to be completely reliable, especially after specimen retrieval, nor are they readily available. In the current study, a novel technique has been described for full wall thickness esophagotomy closure, using a conventional laparoscopic suture device. Although the esophagotomy closure was not complete with the SILS stitch application, combining it with an esophageal stent provided closure with a good survival rate. Endoscopic signs of incomplete esophageal closure associated with collection were found in three survival experiments, after esophageal stent removal 15 days after the procedure. This might have been too soon for removal of stents; most authors would recommend leaving the esophageal stent in place for at least 6 weeks [28]. Another cause for wound dehiscence with necrotic recess could be related to the fact that the suture was applied longitudinally, rather than in a transverse manner. This resulted in the partial esophageal stricture that was observed during esophageal stent placement. Esophageal stents, with their circumferential strength, are a recognized treatment alternative for esophageal strictures [29]. In fact, none of the pigs in the survival group showed signs of stricture 15 days after surgery, although stricture may have been avoided by stitch rupture in the early postoperative days. Finally, feeding the animals 8 hours after surgery might have been too soon, as this could favor local contamination. Even though the infection associated with wound dehiscence was confined and separated from both the pericardium and lungs, the high incidence of esophageal wound dehiscence makes us reluctant to suggest this closure method at this stage. Further development of endoscopic devices will provide safer solutions in the future.

Survival experiments were essential to prove that transesophageal pulmonary lobectomy was not only feasible but also reliable. Even without any thoracic tube drainage, other than the one performed immediately after esophageal closure, and without any postoperative respiratory support, all the animals survived, with no thoracic sequelae besides local pleural adhesions. Infection was prevented by a 3-day antibiotic regimen, and no pulmonary or pericardial complications were noted, other than local pleural adhesions. Again, by using a hybrid NOTES approach, it was possible to perform major thoracic surgery both safely and reliably in the porcine model. The animal model is certainly a limitation of the current study; in fact the porcine anatomy is somewhat different from the human anatomy. The independent right upper bronchus emerging directly from the trachea facilitates its dissection and ligation using the endoscopic stapler coming from the esophagus. Furthermore, human cadaver studies are not possible for procedures in the lung. This is the main reason why all published transesophageal NOTES procedures have been performed in the porcine model [1 – 12].

Results from the acute study demonstrated that transesophageal NOTES, with the assistance of a single transthoracic trocar, can be used for highly complex thoracic procedures. Moreover, the survival protocol confirmed the reliability of the procedure, and it must be stressed, without any special care frequently used for thoracic interventions – minimal aseptic precautions, no thoracic drain left in place, no intensive care support, and almost immediate food ingestion ad libitum.

In conclusion, transesophageal right upper pulmonary lobectomy using single transthoracic trocar assistance is feasible and may represent a step towards scar-free pulmonary lobectomy.

Competing interests: J. Correia-Pinto is a consultant for Karl Storz GmbH.

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Acknowledgment

This project was funded by the FCT Grants project PTDC/SAU-OSM/105578/2008.

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Chapter 3 | HYBRID THORACIC NOTES LEFT ATRIAL APPENDAGE LIGATION

3. Hybrid thoracic NOTES left atrial appendage ligation

Moreira-Pinto J, Ferreira A, Miranda A, Rolanda C, Correia-Pinto J. Left atrial appendage ligation with single transthoracic port assistance: a study of survival assessment in a porcine model (with videos). Gastrointest Endosc 2012; 75: 1055-1061.

ORIGINAL ARTICLE

Left atrial appendage ligation with single transthoracic port assistance: a study of survival assessment in a porcine model (with videos)

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Background: Left atrial appendage (LAA) exclusion is a well-known procedure for the prevention of stroke in high-risk patients with atrial fibrillation and contraindication to long-term oral anticoagulant therapy.

Objective: To evaluate a natural orifice transluminal endoscopic surgery (NOTES) approach for LAA ligation.

Design: In 4 acute and 6 survival pigs, we performed LAA by using a forward-viewing, single-channel gastroscope and an operative thoracoscope with a 3-mm working channel (introduced through an 8-mm single transthoracic port).

Setting: Animal laboratory.

Interventions: The gastroscope was introduced in the thoracic cavity through an esophageal submucosal tunnel. An end loop introduced through the gastroscope was used to legate the LAA. In the survival experiments, the esophageal mucosa was closed using hemoclips.

Main Outcome Measurements: The time, safety, and feasibility of the procedure were recorded. In the survival experiments, endoscopy and postmortem examination were performed on postoperative day 14.

Results: Creation of a submucosal tunnel and esophagotomy were safely performed in all animals without incidents. The mean time for esophagotomy was 17.0 ± 6.3 minutes. Pericardial dissection and LAA ligation were performed in all animals but 1. The mean time for LAA ligation was 34.4 ± 19.1 minutes. No adverse events occurred during the survival period. Endoscopy showed complete esophageal closure. Postmortem examination revealed pleural adhesions on the site of pericardial dissection, and the LAA was fibrotic with the endoloop in place.

Limitations: Animal study.

Conclusions: LAA ligation with single transthoracic trocar assistance is feasible and may be an alternative to anticoagulant therapy or to permanent intracardiac implants in patients with atrial fibrillation. (Gastrointest Endosc 2012;xx:xxx.)

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 6 million people worldwide.[1] AF increases the risk of stroke by 4- to 5-fold in nonrheumatic patients[2] and by 17-fold in the setting of rheumatic mitral stenosis.[3] It is responsible for 10% of all ischemic strokes and half of all cardioembolic strokes.[4] Although anticoagulation therapy is effective, alternative means to avert the risk of stroke from thromboembolism

Abbreviations: AF, atrial fibrillation; IM, intramuscularly; LAA, left atrial appendage; NOTES, natural orifice transluminal endoscopic surgery.

DISCLOSURE: *The following author disclosed a financial relationship relevant to this publication: Dr Correia-Pinto, consultant to Karl Storz. The other authors disclosed no financial relationships relevant to this publication. This project was funded by the Grants FCT project PTDC/SAU-OSM/105578/2008.*

0016-5107/$36.00
doi:10.1016/j.gie.2011.12.018

Received October 13, 2011. Accepted December 16, 2011.

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are being studied because of the need for monitoring, the risk of bleeding complications, and the potential for drug interactions.[5]

Several studies found a predilection for thrombus to form in the left atrial appendage (LAA) in patients with AF because of the increase in its size and flow pattern alteration.[6] Thus, several methods to occlude the LAA have been assessed to decrease stroke burden. Open-surgery LAA ligation has been widely assessed for feasibility, safety, and efficacy in stroke prevention.[7] Thoracoscopic LAA ligation has been described with similar results.[8] In 2002, Sievert et al[9] presented the technique for LAA occlusion using a percutaneous endovascular device that delivers an expandable cage into the LAA, preventing blood to flow inside it. Since then, several percutaneous devices have been developed and are currently being tried.[5] Although these percutaneous devices show promising results, several possible complications remain (pericardial effusion, air embolism, device migration, pseudoaneurysm, infection, and device thrombus formation). There are also some limitations (LAA size and variable anatomy) that demand, in specific cases (eg, size disproportion or distorted anatomy of LAA), the development of alternative surgical techniques for LAA ligation.[10]

With the recent developments in natural orifice transluminal endoscopic surgery (NOTES), one should be aware that new approaches to the thorax are emerging as alternatives to the classic thoracoscopic surgery. In 2007, Sumiyama et al[11] proposed a transesophageal access to the thoracic cavity. Since then, transesophageal NOTES has been tested for several simple thoracic procedures in a porcine model.[12-18] Moreover, EUS and FNA of transesophageal lesions are established diagnostic techniques in gastroenterology and are now also used for therapeutic purposes. With the proximity of the heart to the esophagus and the utility of the diagnostic technique of transesophageal echocardiography in mind, Fritcher-Ravens et al[19] tested introducing a needle through the esophagus wall and the posterior cardiac wall into the left atrium and beyond, as far as the aortic valve, with success in a porcine model. Considering transesophageal access for performing cardiac surgery, surgeons can see some hurdles. First, the possible mechanical abrasion of and trauma to surrounding structures while performing an inside-out esophagotomy. Moreover, an ineffective esophagotomy closure can be devastating, with serious infectious complications. Finally, tissue manipulation and suturing can be challenging when using flexible parallel instruments from the conventional gastroscope. Rolanda et al[20] recently proposed the combination of a single transthoracic trocar with transesophageal NOTES to increase the safety and feasibility of more complex procedures.

We hypothesized that thoracic NOTES might be indicated in ultraminimally invasive LAA ligation, independently of the size or distorted anatomy of LAA. Thus, we designed this research protocol to assess the feasibility and reliability of peroral transesophageal LAA ligation with the assistance of a single transthoracic trocar.

Take-home Message

- Transesophageal natural orifice transluminal endoscopic surgery with single transthoracic assistance (with or without transesophageal US monitoring) might be the key to human translation of simple thoracic procedures.
- Transesophageal left atrial appendage might be a good alternative to percutaneous endovascular techniques.

MATERIAL AND METHODS

Study design

Ten female pigs (*Sus scrofus domesticus*) weighing 25 to 35 kg were used to perform transesophageal LAA ligation with the assistance of a single transthoracic trocar. Ten consecutive in vivo experiments were undertaken (4 acute and the last 6 animals for survival assessment). All surgical endoscopic and thoracoscopic procedures were recorded. Vital signs and physiological parameters were monitored during the experiment. The procedure time was recorded as well as difficulties and complications at each step of the procedure. The animals in the survival group were monitored for 14 days. Endoscopic examination and necropsy were performed in all animals at the end of the protocol (after the procedure in the acute animals and after the survival animals were killed). This study was approved by the ethical review board of Minho University (Braga, Portugal).

Pig preparation

All procedures were performed with the animals under general anesthesia with endotracheal intubation and mechanical ventilation (Fig. 1). The pigs had no food (8 hours) or water (4 hours) before the surgery. The pigs were premedicated with a combination of azaperone (4 mg/kg, intramuscularly [IM]), midazolam (1 mg/kg, IM), and atropine (0.05 mg/kg, IM). Anesthesia was induced with propofol (6 mg/kg, intravenously) and maintained with continuous propofol infusion (20 mg/kg/h, intravenously) and buprenorphine (0.05 mg/kg, IM).

Surgical technique

The main steps of the procedure described here are schematically illustrated in Figure 2. The pig was placed in the dorsal decubitus position. An 8-mm trocar (C0Q61, Kii Shielded Bladed Access System; Applied Medical, Rancho Santa Margarita, Calif) was inserted in the fourth intercostal space in the left anterior axillary line. CO_2 was inflated through the transthoracic trocar, and pressure was maintained up to 6 mm Hg. An operative thoracoscope with a 3-mm working channel (Hopkins Wide-Angle Straight For-

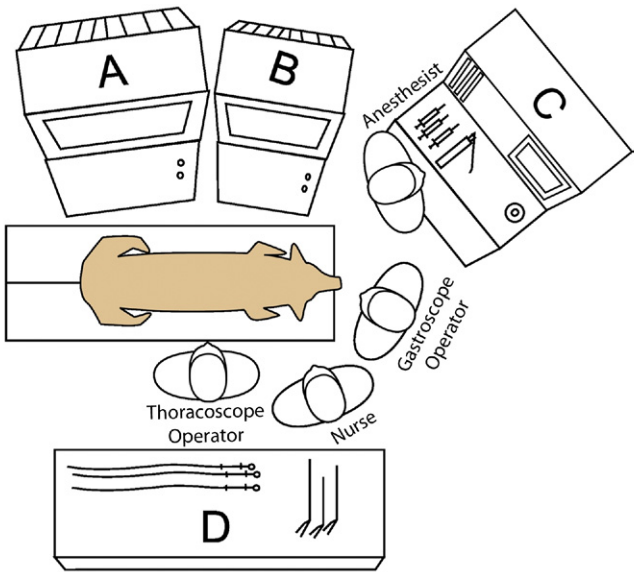

Figure 1. Room ergonomics. **A,** Thoracoscope monitor. **B,** gastroscope monitor. **C,** Ventilator. **D,** Back table for equipment.

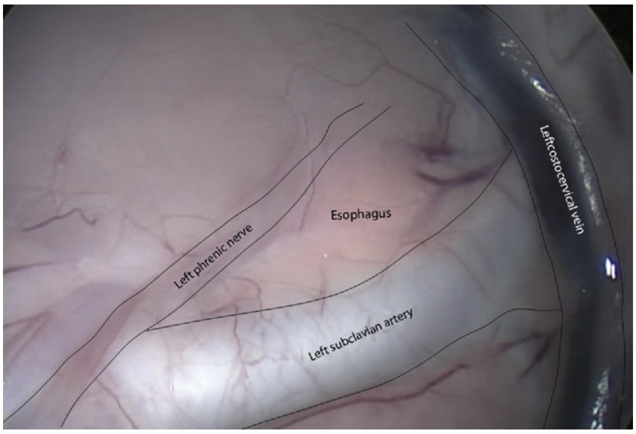

Figure 2. Thoracoscopic anatomy of the esophagotomy site.

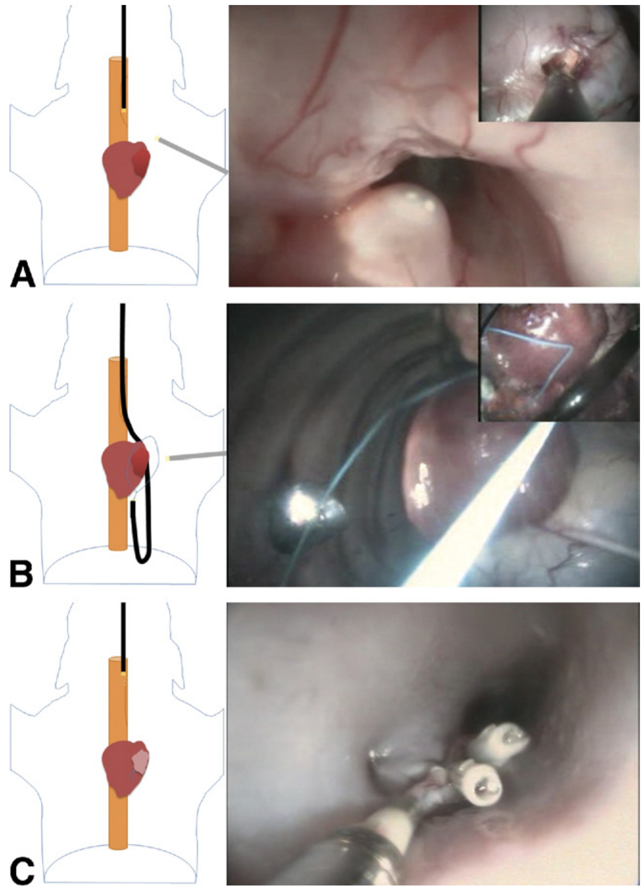

Figure 3. Steps for transesophageal left atrial appendage ligation. Main image represents gastroscopic view, and insets (**A, B**) represent thoracoscopic view. **A,** Gastroscope going through the submucosal tunnel and thoracoscope showing the exact site for esophagotomy. **B,** Endoloop going through the gastroscope working channel and thoracoscopic positioning of the LAA inside it. **C,** Closing the mucosal incision of the esophagus with 3 hemoclips.

ward Telescope 6 Degrees, 27092AMA; Karl Storz, Tuttlingen, Germany) was introduced through the trocar. By using a rigid dissector (30310MLG; Karl Storz), we dissected the upper mediastinum and identified the esophagus, with the help of gastroscope movements (inside the esophagus) and transillumination, between the left phrenic nerve, the left costocervical vein, and the left subclavian artery (Fig. 3).

A forward-viewing, single-channel gastroscope (13801PKS; Karl Storz) was advanced into the esophagus, identifying the position of the thoracoscope and the esophagotomy site. Five milliliters of saline solution were injected into the submucosa 8 cm proximal to the esophagotomy position, by using an injection needle (110231-01; Karl Storz), and a 1-cm longitudinal incision was made in the mucosa using a needle-knife (KD-11Q-1; Olympus, Tokyo, Japan) through the gastroscope working channel. Then an 8- to 9-cm long submucosal tunnel was created by blunt dissection. Esophagotomy was performed in the distal part of the submucosal tunnel (in the upper third of the esophagus). All transesophageal procedures were performed under gastroscopic and thoracoscopic image control.

The pericardium was incised above the LAA, avoiding the left phrenic nerve, using a rigid grasper (27290K; Karl Storz) inserted through the thoracoscope working channel for traction and the needle-knife with cautery through the gastroscope for cutting. To further dissect the pericardium, we inverted the positions. A flexible grasper (11252MX; Karl Storz) and rigid 3-mm scissors (30310MW; Karl Storz) were inserted through the working channels of the gastroscope and thoracoscope, respectively.

After delimiting and externalizing the LAA by using a rigid atraumatic grasper (30310ONG; Karl Storz) introduced through the thoracoscope, the LAA was ligated by using a nylon endoloop (disposable ligation device HX-400U-30; Olympus) introduced through the gastroscope and positioned with the help of a thoracoscopic grasper.

In the survival group, in addition to the surgical procedure described, the esophageal mucosa was closed at the

TABLE 1. Results of 4 acute and 6 survival experiments

Experiment	Esophagotomy: min, complications	Pericardium incision and LAA ligation: min, complications	Esophagotomy closure: min, complications	Acute vs survival
1	20	25	—	Acute
2	25	20	—	Acute
3	30, small thymus hemorrhage during pleural dissection solved without the need for coagulation	30, small LAA wall hemorrhage during manipulation solved without the need for coagulation	—	Acute
4	15	—, iatrogenic rupture of LAA because of traumatic grasper misuse	—	Acute (interrupted at 35 min)
5	15	30	5	Survival (14 d)
6	15	45, small LAA wall hemorrhage during manipulation, solved without the need for coagulation	15	Survival (14 d)
7	10	60, small LAA wall hemorrhage during manipulation, solved without the need for coagulation	15	Survival (14 d)
8	15	5	5	Survival (14 d)
9	10	30	10	Survival (14 d)
10	15	65, incomplete LAA ligation because of previous pericardial adhesions	10	Survival (14 d)

LAA, Left atrial appendage; —, not available.

proximal edge of the submucosal tunnel by using 3 flexible hemoclips (EZ Clip HX-110LR; Olympus). At the end of the procedure, the pericardium was left open, and the pneumothorax was drained by using a thoracic tube introduced through the transthoracic trocar. No drain was left in place after the intervention. The trocar skin incision was sutured with 2 nonabsorbable independent stitches.

Postoperative care (survival group)

At the end of the surgical intervention, all animals received a single dose of buprenorphine (0.05 mg/kg, IM) and meloxicam (0.4 mg/kg, IM). Antibiotic ceftiofur hydrochloride (5 mg/kg, IM) was repeated at 24-hour intervals for 3 consecutive days. A regular diet was resumed 8 hours after surgery. The animals were closely monitored for any signs of postoperative complications, distress, behavior changes, anorexia, or weight loss. After the follow-up period, the animals were anesthetized for endoscopic examination. Then they were killed, and necropsy was performed to check for LAA complete ligation, healing of the esophagotomy, and signs of cardiac or pulmonary complications.

RESULTS

The overall results of our study are summarized in Table 1. Dorsal decubitus and the CO_2 insufflation permitted good visualization of the heart and the pericardium up to the apex. Coordinating the images from the thoracoscope and gastroscope allowed us to determine the ideal site for esophagotomy. Submucosal tunnel creation and esophagotomy were performed safely without incident in all animals (Fig. 3A; Video 1, available online at www.giejournal.org). The mean time to perform the esophagotomy was 17.0 ± 6.3 minutes.

Pericardial opening and complete LAA ligation were performed without significant problems in all but 2 animals (Fig. 3B; Video 2, available online at www.giejournal.org). Ligation was achieved by coordinating both thoracoscopic and gastroscopic images and instruments with minimal mobilization of the LAA. As the endoloop was introduced from the apex by using the gastroscope in a retroflexed position, the atraumatic grasper through the thoracoscope adjusted the upper part of the LAA inside the loop. In experiment 4, misuse of the conventional grasper to

Figure 4. Esophageal mucosa scar 14 days postoperatively.

manipulate LAA caused tearing of the LAA. The hemorrhage was controllable by grasping the perforation with the atraumatic grasper, but the animal died, and we terminated the experiment. In the last experiment, pericardial adhesions from a previous infection did not permit a good dissection of the LAA, and only partial ligation was achieved. The mean time for LAA ligation was 34.4 ± 19.1 minutes.

The instruments entering through both the gastroscope and thoracoscope created a triangulation very similar to the one experienced with the exclusively thoracoscopic approach. The flexible endoscope had good access to all aspects of the heart by using a direct position to reach the base of the heart and retroflexion for its apex. Moreover, a flexible gastroscope was useful in showing some parts of the thoracic cavity that could not be visualized with the 6-degree optic of the operative thoracoscope, ie, the lateral thoracic wall and the entire diaphragm.

With exception of the acute experiment that was terminated because of LAA rupture, all of the other animals were kept alive until the end of the experiment. LAA ligation was verified on necropsy.

In the survival group, the esophageal mucosa was closed by using endoscopic clips (Fig. 3C; Video 3, available online at www.giejournal.org), and the thoracotomy was sutured after pneumothorax drainage. The mean time to close was 10.0 ± 4.5 minutes. The total mean operating time in the survival group was 62.5 ± 25.1 minutes. All 6 animals in the survival group lived for 14 days. After recovering from anesthesia, the pigs tolerated a regular diet started 8 hours after surgery and ambulated freely, exhibiting normal behavior. No adverse event occurred during the survival period. Endoscopic examination before killing revealed complete esophageal closure in all animals (Fig. 4). No esophageal strictures were found. Postmortem examination revealed pleural adhesions on the site of pericardial dissection, and the LAA was fibrotic with the nylon endoloop in place (Fig. 5). There were no signs of infection in the ipsi- or contralateral pleural space and lung parenchyma.

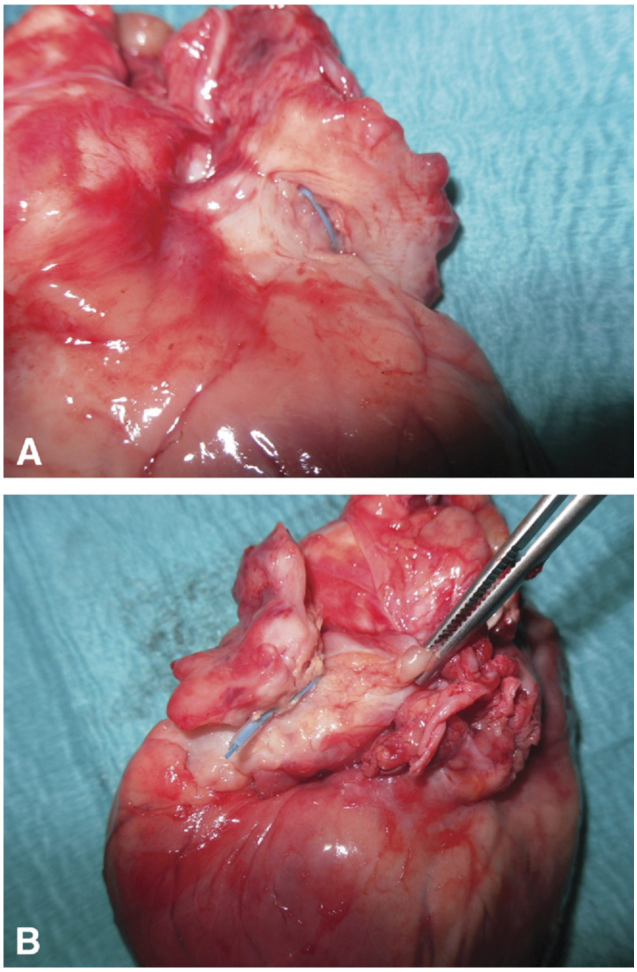

Figure 5. Heart view showing fibrotic left atrial appendage 14 days after ligation with the endoloop in place. **A,** Anterior view. **B,** Posterior view.

DISCUSSION

LAA ligation is a well-known procedure for the prevention of strokes in high-risk patients with AF and a contraindication to long-term oral anticoagulant therapy. Open surgery is highly invasive and is only performed in patients requiring other cardiac surgery such as mitral valve surgery and maze procedures.[5] Ligation of the LAA can also be performed thoracoscopically using an endoloop or stapling device with similar results.[8]

Recently, percutaneous catheter-based systems to occlude the LAA have been presented. The Amplatzer Septal occluder (AGA Medical Corporation, Golden Valley, Minn), which was originally described for patent foramen ovale or atrial septal defect closure, evolved into the Amplatzer Cardiac Plug (AGA Medical Corporation) and is currently being compared in a clinical trial.[5,9] The PLAATO system (eV3 Inc, Plymouth, Minn) is a self-expanding nitinol cage coated with a polytetrafluoroethylene membrane that ensures endothelialization of the implant.[21] The WATCHMAN Device (Atritech Inc, Plymouth, Minn) is also a self-expanding nitinol cage with a permeable polyester fabric covering the surface exposed to the left atrium.[22] Although the first reports regarding percutaneous LAA occlusion show encouraging results, several possible complications still remain.[5,20-22] These include air embolism, device embolization, perforation, device malposition, residual shunt, arrhythmia, infection, and thrombus formation on the device.[23] Moreover, a large and distorted LAA cannot be completely occluded by endovascular devices. For these cases, alternative external LAA ligation techniques are being developed. In 2010, Lee et al[10] reported a catheter-based LAA ligation technique using a minimally invasive surgical pericardial window created to access the pericardial space.

In the NOTES era, transesophageal endoscopic surgery is emerging as an alternative to the classic thoracoscopic surgery. The theoretical advantages of NOTES over open surgery and conventional thoracoscopy include decreased postoperative pain, reduction/elimination of general anesthesia, performance of procedures in an outpatient or even office setting, and possible cost reduction. Moreover, eliminating a skin incision avoids associated complications such as wound infections and hernias, and facilitates a shorter hospital stay, faster return to regular activity, improved cosmetic outcomes, and increased overall patient satisfaction. Recently, Rolanda et al[20] introduced the concept of hybrid thoracic NOTES. By introducing a transthoracic trocar, the authors overcame some potential risks of the transesophageal approach, ie, blind esophagotomy creation, esophagotomy closure, thoracic drainage at the end of the procedure, and triangulating instruments. Transesophageal NOTES with single transthoracic assistance (with or without transesophageal US monitoring) might be the key to human translation of simple thoracic procedures, ie, LAA ligation.

As discussed earlier, the supine position allows gravity to provide good cardiac exposure with minimal handling. We did not need to retract the lung and that allowed us to focus the transthoracic instruments on the surgical procedure. We found the thoracic trocar very useful for CO_2 inflation and for its pressure control. Also, the transthoracic trocar permitted the control of esophagotomy, performed from the inside-out of the esophagus, pointing out the exact place where it should be created, side and level, and avoiding lesions of arteries, veins, and nerves. Finally, when the procedure was completed, the trocar site was used for tube insertion and acute pleural drainage.

Combining 2 opposite sites, for insertion of the gastroscope and thoracoscope and respective instruments, we could obtain regular triangulation and countertraction that simulates the 2 hand movements of the surgeon. This promoted secure manipulation of tissues, careful dissection of the pericardium, and effective LAA ligation. The only LAA perforation that we had during the study was caused by the misuse of a traumatic grasper instead of using the atraumatic one that occurred in the first nonsurvival experiments. We did not experience this complication while using the atraumatic grasper. However, if this were to happen in a human, we believe that conversion to open surgery would be the best option. Again, the fact that we have a gastroscope inside the thorax may permit control of the hemorrhage by grasping the orifice or occluding it with a balloon, while an emergency sternotomy is performed. As mentioned earlier, the flexible endoscope inside the thorax allows visualization of the entire cavity including sites where rigid transthoracic endoscopes cannot reach, ie, the base and apex of the heart, identifying the limits of the LAA neck, even in large distorted ones.

Regarding the esophagotomy technique, various solutions for endoscopic esophagotomy closure have been suggested. Opening the muscular layer after a submucosal tunnel is created may not even require closing the mucosa.[9,16] We opted to close the mucosa with clips, and this technique was found to be reliable and quite effective in all of our survival experiments. Mediastinal and lung infection could be of some concern. The submucosal tunnel before esophagotomy creates a valve system that collapses as soon as the procedure is completed. As shown in our experiments, combining the esophageal submucosal tunnel with antibiotic prophylaxis is enough to avoid any type of infection.

Follow-up transesophageal US studies have found that surgical LAA occlusion is incomplete in between one third to one half of cases in patients undergoing LAA ligation via open surgery.[7,25] In these studies, either regular nonabsorbable suture or staplers were used. None of these studies used a nylon endoloop for LAA ligation. In our study, necropsy revealed complete LAA ligation in all acute experiments, and full ligation with fibrotic LAA in all but 1 of the survival studies. However, as reported earlier, previous pericardial adhesions (eg, caused by previous thoracic intervention) might be a limiting factor for LAA dissection and full ligation when using our technique.

The animal model certainly is a limitation of our study, although the cardiac porcine anatomy is very similar to that of humans. Even so, survival experiments were essential to prove that transesophageal LAA ligation was not only feasible but reliable. Even without thoracic tube drainage, other than immediately after esophageal closure, all animals survived, with no thoracic sequelae except for minor local adhesions. Again, by using a hybrid NOTES approach we managed to perform LAA ligation safely and reliably.

Our results proved that transesophageal NOTES, with the assistance of a single transthoracic trocar, can be used for cardiac procedures. We believe that transesophageal LAA could be indicated in patients with AF who do not want or cannot be on anticoagulant therapy. Transesophageal LAA might be a good alternative to percutaneous endovascular techniques, especially in patients who have large distorted LAA and are contraindicated for LAA occlusion with expandable devices or catheter-based ligation.[24] Another advantage of transesophageal LAA ligation over percutaneous techniques is avoiding exposure of patients and health providers to unnecessary radiation from fluoroscopy.[26]

Finally, transesophageal LAA ligation can be the first step to more complex cardiac NOTES procedures, for instance, the maze procedure, which has been the criterion standard for the treatment of symptomatic drug-refractory AF and was recently performed by the thoracoscopic approach.[27] Considering the described achievements, we propose that that our hybrid approach could be safely used in humans in what we believe to be a step forward in minimally invasive cardiac surgery. Clinical trials are necessary to determine whether this procedure should be generally applied and whether its potential benefits are actually superior to those of percutaneous techniques.

In conclusion, transesophageal LAA ligation by using single transthoracic trocar assistance is feasible and may represent a minimally invasive option for LAA ligation.

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Chapter 4 | **HYBRID THORACIC NOTES**

THYMECTOMY

4. Hybrid thoracic NOTES thymectomy

Moreira-Pinto J, Ferreira A, Miranda A, Rolanda C, Correia-Pinto J. Hybrid endoscopic thymectomy: combined transesophageal and transthoracic approach in a survival porcine model with cadaver assessment.

SURGICAL ENDOSCOPY and Other Interventional Techniques

Springer

Hybrid Endoscopic Thymectomy: combined transesophageal and transthoracic approach in a survival porcine model with cadaver assessment

Journal:	*Surgical Endoscopy*
Manuscript ID:	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Keyword:	General < Oesophageal, Surgical < Technical, Technical < Endoscopy, Thoracoscopy
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[Title Page]

HYBRID ENDOSCOPIC THYMECTOMY:

combined transesophageal and transthoracic approach in a survival porcine model with cadaver assessment

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Support: This project was funded by the FCT Grants project PTDC/SAU-OSM/105578 /2008.

Disclosures: J. Correia-Pinto is a consultant for Karl Storz GmbH. The remaining authors have no competing interests.

Running Title: Hybrid endoscopic thymectomy.

[Abstract]

Backgound: Video-assisted thoracoscopic surgery (VATS) thymectomy has been used in the treatment of Myastenia Gravis and thymomas (coexisting or not). In natural orifice transluminal endoscopic surgery (NOTES), new approaches to the thorax are emerging as alternatives to the classic transthoracic endoscopic surgery. The aim of this study was to assess the feasibility and reliability of hybrid endoscopic thymectomy (HET) using a combined transthoracic and transesophageal approach.

Methods: Twelve consecutive in vivo experiments were undertaken in the porcine model (4 acute and 8 survival). The same procedure was assessed in a human cadaver afterwards. For HET, an 11 mm trocar was inserted in the 2^{nd} intercostal space in the left anterior axillary line. A 0º 10 mm thoracoscope with a 5 mm working channel was introduced. Transesophageal access was created through a submucousal tunnel using a flexible gastroscope with a single working channel introduced through the mouth. Using both flexible (gastroscope) and rigid (thoracoscope) instruments, the mediastinum was opened, the thymus was dissected and the vessels were ligated using electrocautery alone.

Results: Submucosal tunnel creation and esophagotomy were performed safely without incidents in all animals. Complete thymectomy was achieved in all experiments. All animals in the survival group lived for 14 days. Thoracoscopic and postmortem examination revealed pleural adhesions on site of the surgical procedure with no signs of infection. Hystological analysis of the proximal third of the esophagus revealed complete cicatrization of both mucosal defect and myotomy site. In the human cadaver, we were able to replicate all the procedure even though we were not able to identify the thymus.

Conclusions: HET is feasible and reliable. HET could be regarded as a possible alternative to classic thoracoscopic approach for patients requiring thymectomy.

[Introduction]

Video-assisted thoracoscopic surgery (VATS) was first described in the early 1990's. Initial applications included chest exploration, pleural effusion or pneumothorax management, and limited resection of lung nodules [1-4]. As minimally invasive techniques improved, clinical application of VATS became progressively widespread for more complex procedures. VATS thymectomy was first described by Landreneau et al in 1992 [5]. VATS thymectomy offers benefits of reduced immune-mediated surgical stress response and less chest trauma, with reduced impairment of postoperative pulmonary function that translates to faster recovery and fewer complications [6, 7]. VATS thymectomy has been used for Myasthenia Gravis and for both well-encapsulated noninvasive thymomas and selected invasive thymomas [8-10].

In natural orifice transluminal endoscopic surgery (NOTES), new approaches to the thorax are emerging as alternatives to classic transthoracic endoscopic surgery. In 2007, Sumiyama *et al.* proposed transesophageal access to the thoracic cavity [11]. Since then, transvesical-transdiaphragmatic [12], transgastric-transdiaphragmatic [13], and transtracheal thoracoscopy [14] have also been suggested. The transesophageal approach has been considered preferable as a direct entry to the thorax and posterior mediastinum for several simple thoracic procedures in porcine models [15]. However, the transesophageal approach is typically considered to be highly risky because of possible mechanical abrasion and trauma of surrounding structures. Moreover, an ineffective esophagotomy closure can be devastating, resulting in serious infectious complications. In fact, some of the recognized difficulties of NOTES procedures, such as safe port creation, infection prevention, tissue manipulation, suturing and anastomosis establishment, seem to be particularly relevant in the transesophageal approach. In view of this, Rolanda et al. proposed the combination of single transthoracic trocar assistance with transesophageal NOTES in order to increase the safety and feasibility of more complex procedures [16]. Since then, our group has proven the safety and feasibility of hybrid transesophageal pulmonary lobectomy [17] and hybrid transesophageal left atrial appendage ligation [18] in the survival porcine model.

We hypothesized that thoracic NOTES might be appropriate for thymectomy. Thus, we designed this research protocol to assess the feasibility and reliability of hybrid endoscopic thymectomy (HET) using combined transthoracic and transesophageal approach.

[Methods]

Study design

Twelve female pigs (Sus scrofus domesticus) weighting 25 to 35 kg were used to perform HET. Consecutive *in vivo* experiments were undertaken (4 acute and 8 survival assessments). All surgical gastroscopic and thoracoscopic procedures were recorded. Vital signs and physiological parameters were monitored during the experiment. The procedure time was recorded as well as difficulties and complications at each step of the procedure. The retrieved specimens were analyzed under a microscope to check if there was complete resection of the thymus. The animals in the survival group were monitored for 14 days. Gastroscopic and thoracoscopic examination and necropsy were performed in all animals at the end of the protocol (after the procedure in the acute animals and 14 days after when the survival animals were killed). The proximal esophagus of the pigs in the survival group were analyzed under a microscope to verify the healing process.

After the animal experiments, we performed the same procedure in a human female cadaver. Gastroscopic and thoracoscopic videos were recorded. The procedure time was recorded as well as difficulties and complications at each step of the procedure.

This study was approved by the ethical review board of Minho University (Braga, Portugal).

Pig preparation

All procedures were performed with the animals under general anesthesia with endotracheal intubation and mechanical ventilation. The pigs had no food (8 hours) or water (4 hours) before surgery. The pigs were premedicated with a combination of azaperone (4 mg/kg, intramuscularly [IM]), midazolam (1 mg/kg, IM), and atropine (0.05 mg/kg, IM). Anesthesia was induced with propofol (6 mg/kg, intravenously [IV]) and maintained with continuous propofol infusion (20 mg/kg/h, IV) and buprenorphine (0.05 mg/kg, IM). The pig was placed in the dorsal decubitus position.

Human cadaver preparation

A 72 year old-female human cadaver weighting 75 kg was defrosted 48 hours prior to the operation. The cadaver was placed in the dorsal decubitus position with her left arm abducted.

Surgical technique (animal model and Human cadaver)

The main steps of the procedure described here are schematically illustrated in Figure 1. An 11-mm trocar (CTF33, Kii Access System; Applied Medical, Rancho Santa Margarita, California) was inserted in the second or third intercostal space in the left anterior axillary line. Carbon dioxide (CO_2) was inflated through the transthoracic trocar, and pressure was maintained up to 6 mm Hg. An operative thoracoscope with a 5-mm working channel (Straight Forward Telescope 0º 26034AA; Karl Storz GmbH, Tuttlingen, Germany) was introduced through the trocar. By using a rigid dissector (30310MLG; Karl Storz), the upper mediastinum was dissected allowind the identification of the esophagus with the help of gastroscope movements (inside the esophagus) and transillumination, between the left phrenic nerve, the left costocervical vein, and the left subclavian artery (Figure 1A).

A forward-viewing, single-channel gastroscope (13801PKS; Karl Storz) was advanced into the esophagus, identifying the position of the thoracoscope and determining the esophagotomy site. Five milliliters of saline solution were injected into the submucosa 8 cm proximal to the esophagotomy position using an injection needle (110231-01; Karl Storz), and a 1-cm longitudinal incision was made in the mucosa using a needle-knife (KD-11Q-1; Olympus, Tokyo, Japan) through the gastroscope working channel. Next an 6- to 8-cm long submucosal tunnel was created by blunt dissection. Esophagotomy was performed in the distal part of the submucosal tunnel (in the upper third of the esophagus).

While the submucosal tunnel was created in the esophagus, the left mediastinal pleura was opened and the left posterior limits of the thymus dissected using rigid instruments introduced through the transthoracic trocar. Once the transesophageal access was created, the dissection of the thymus was completed using both flexible (gastroscope) and rigid (thoracoscope) instruments (Figure 2B). The vessels were ligated using electrocautery alone, either through the flexible coagulation grasper (gastroscope) or the rigid dissector (thoracoscope). All endoscopic procedures were performed under gastroscopic and thoracoscopic image control.

The specimens were retrieved through an endoscopic bag (Endopouch Retriever, Ethicon Endo-Surgery, Cincinnati, Ohio, USA) introduced through the transthoracic trocar. For this, the surgeon handling the gastroscope grasped the specimens and put it inside the endoscopic bag (Figure 1C).

In the survival group, in addition to the surgical procedure described, the esophageal mucosa was closed at the proximal edge of the submucosal tunnel using 4 to 5 flexible hemoclips (EZ Clip HX-110LR; Olympus). At the end of the procedure, the pneumothorax was drained using a thoracic tube introduced through the transthoracic trocar. No drain was left in place after the intervention. The trocar skin incision was sutured with 2 independent knots of non-absorbable stitches.

Postoperative care (survival animal group)

At the end of the surgical intervention, all animals received a single dose of buprenorphine (0.05 mg/kg, IM) and meloxicam (0.4 mg/kg, IM). Antibiotic ceftiofur hydrochloride (5 mg/kg, IM) was repeated at 24-hour intervals for 3 consecutive days. A regular diet was resumed 8 hours after surgery.

The animals were closely monitored for any signs of postoperative complications, distress, behavior changes, anorexia, or weight loss. After the follow-up period, the animals were anesthetized for gastroscopic and thoracoscopic examination. They then were killed and necropsy was performed to check for signs of cardiac or pulmonary complications. The proximal esophagus was analysed under a microscope to verify the healing process.

[Results]

Animal model

The overall results of our study are summarized in Table I. Dorsal decubitus and CO_2 inflation permitted good visualization of the upper mediastinum. The coordination of the images from the thoracoscope and gastroscope allowed the determination of the ideal site for esophagotomy. Submucosal tunnel creation and esophagotomy were performed safely without incidents in all animals (Figure 1A; Video 1). The mean time to perform the esophgotomy was 12.8 +/- 3.0 minutes.

While the gastroscope operator was performing the submucosal tunnel, the surgeon with the thoracoscope opened the mediastinal pleura and began dissection of the left posterior limits of the thymus. We found that working with a single instrument without triangulation to be very limiting in terms of dissection. Nevertheless, leaving the anterior plane intact allowed the suspension of the thymus, facilitating the dissection of the posterior aspect when working together with the gastroscopic flexible instruments.

As soon as a transesophageal access was created, the instruments entering through both the gastroscope and thoracoscope created a triangulation very similar to the one experienced with the exclusively thoracoscopic approach. The flexible endoscope in retroflexion was essential for traction and conter-traction of the thymus. Lifting the thymus permitted a good dissection with the rigid dissector entering through the thoracoscope working channel. Pushing the thymus down was critical to separate it from the vessels in the upper medistinum (Figure 1B; Video 2). The flexible gastroscope was also useful for showing some parts of the thoracic cavity that could not be visualized with the 0-degree optic of the operative thoracoscope, ie, the lateral thoracic wall and the entire diaphragm. Finally, retrieval of the specimens through an endoscopic bag introduced through the thoracic wall was only possible because the gastroscope gave visual control of the bag inside the chest and allowed the introduction of a grasper that was used to put the specimens inside the bag (Figure 1C; Video 3).

As reported in Table I, there were only minor incidents during endoscopic thymectomy. Small tears in the pericardium and in the counterlateral pleura did not have clinical impact on the animal well-being and did not implicate suturing. As for experiment 11, where a larger amount of pleura was ressected along with the thymus, hemodynamic instability was noted, but the pig recovered rapidly when we stopped CO_2 inflation. We achieved complete thymectomy in one piece in all experiments but one. In experiment number 9, two small pieces were resected. We safely retrieved the specimens using an endoscopic bag in all experiments (Figure 2). The mean time to thymus dissection and retrieval was 35.33 +/- 11.4 minutes. Complete thymus resection was achieved in all animals as verified by histological analysis (Figure 3). Average specimens weight was 10.5 +/- 5.4 gram.

In the survival group, the esophageal mucosa was closed using hemostatic clips (Fig. 3D; Video 4). Thoracotomy was sutured after pneumothorax drainage. The mean time to esophageal mucosa closure was 8.8 +/- 3.4 minutes. The total mean operative time in the survival group was 53.1 +/- 14.4 minutes.

All 10 animals in the survival group lived for 14 days. After recovering from anesthesia, the pigs tolerated a regular diet started 8 hours after surgery and deambulated freely, exhibiting normal behavior. No adverse events occurred during the survival period. Gastroscopic examination before sacrifice revealed complete esophageal closure in all animals. No esophageal strictures were found. In one of the animals two esophageal hemoclips were still in place (Figure 4).

Thoracoscopic and postmortem examination revealed pleural adhesions at the site of the surgical procedure (Figure 5). There were no signs of infection in the ipsi- or contralateral pleural space and lung parenchyma. Histological analysis of the proximal third of the esophagus revealed complete cicatrization of both the mucosal defect and the myotomy site in all the animals (Figure 6).

Human cadaver

We found thoracoscopic visualization in the human cadaver very similar to the one we saw in the porcine model (Figure 7A). Submucosal tunnel creation and esophagotomy was performed safely without incidents, besides some difficulties related to dead tissues manipulation. The time to perform the esophgotomy was 23 minutes.

We could not identify the thymus, because of the cadaver's older age. Even though, we dissected all the fat from major structures in the anterior medistinum (Figure 7B). Again, starting dissection posteriorly permitted suspension of the mediastinal fat, facilitating the dissection. Instruments entering both through the gastroscope and thoracoscope allowed good triangulation.

Flexible gastroscope was useful in showing the lateral thoracic wall and the right-side fo the anterior mediastinum. The overall time to mediastinal fat dissection and retrieval was 65 minutes.

[Discussion]

Thymectomy plays an important role in the treatment of Myastenia Gravis and thymomas (that may coexist). Sternal approach for thymectomy has been widely used for decades. VATS thymectomy has great advantage over sternotomy because of avoidance of muscle division and bone fractures, allowing for diminished duration and intensity of pain and shorter time to return to full activity [19]. Previous studies comparing different operative techniques showed that VATS thymectomy produced a long-term clinical outcome equivalent to that of the extended sternal approach, with lower complication rates [20, 21]. Although some of the reports have suggested the need to perform a bilateral VATS, most perform from the right chest [22]. Approach from the left chest can also be used, but the arch of aorta and the brachiocephalic vein might difficult thoracoscopic access [23].

In the NOTES era, transesophageal endoscopic surgery is emerging as an alternative to the classic thoracoscopic surgery. The theoretical advantages of NOTES over open surgery and conventional thoracoscopy include decreased postoperative pain, reduction/elimination of general anesthesia, performance of procedures in an outpatient or even office setting, and possible cost reduction. Additionally, eliminating a skin incision avoids associated complications such as wound infections and hernias, and facilitates a shorter hospital stay, faster return to regular activity, improved cosmetic outcomes, and increased overall patient satisfaction. Rolanda et al introduced the concept of hybrid thoracic NOTES [16]. By introducing a transthoracic trocar, the authors overcame some potential risks of the transesophageal approach, ie, blind esophagotomy creation, thoracic drainage at the end of the procedure, and triangulation of instruments.

We have already described several advantages of using the single transthoracic assistance, in previous reports [17, 18]. First of all, the trocar site is used for CO_2 inflation and pressure control. At the end of the experiments, it permits tube insertion and acute pleural drainage. This port might be important in the human setting, as thoracoscopic procedures always need some time of thoracic drainage. Transthoracic visualization allows control of esophagotomy creation, performed from the inside to the outside of the esophagus, pointing out the exact place where it should be created, side and level, and avoiding lesions of arteries, veins, and nerves. The visual control provided by the thoracoscope permits guiding of instruments introduced transesophageally and manipulated through the mouth.

The concurrent use of two opposite sites for the entrance of scopes and respective instruments allowed for the establishment of regular triangulation and counter-traction thus simulating the two hand movements of the surgeon and promoting secure manipulation of tissues, careful dissection, and effective electrocoagulation for hemorrhagic control. As mentioned before, the flexible endoscope inside the thorax makes possible to examine the whole cavity including sites that rigid transthoracic endoscopes cannot reach – namely the chest wall and counter-lateral mediastinum. Furthermore, the gastroscopic visual control permits guiding of blind-rigid intruments introduced through the transthoracic trocar, as happened with the endoscopic bag. Using the intrathoracic visual control provided by the gastroscope, the surgeon working through the thoracic wall positioned and opened the endoscopic bag. Then, the surgeon handling the gastrosope put the specimens inside the bag. We opted to extract the thymus using this method, because of the risk of disseminating thymus cells along the esophageal submucosal tunnel.

As stated before, most surgeons perform thoracoscopic thymectomy from the right chest or perform bilateral VATS. In our study, thymectomy was done from the left side, because transthoracic visual control for safe esophagotomy was only possible from the left chest. Again, the fact of having a flexible gastroscope entering from the apex permited clear visualization of both sides of the anterior mediastinum and thoracic cavities. So, approaching the thymus from the left was not a limitation in our experiments.

The submucosal tunnel before esophagotomy creates a valve system that collapses as soon as the procedure is completed. Some authors have suggested leaving the mucosal defect open [24]. Mediastinal and lung infection could be of some concern. So we opted to close the mucosa with hemoclips, and this technique was found to be effective in all of our survival experiments. And as shown, combining the esophageal submucosal tunnel with antibiotic prophylaxis was enough to avoid any type of infection.

We always thought the animal model could be a limitation of our study. Although the esophageal and cardio-pulmonary porcine anatomy is very similar to that of humans, the sternum of the pig protudes, resembling pectus carinatum. Suprisingly, we did not find that much difference when performing the hybrid endoscopic approach in the human cadaver. Even though, working space is described as a major hurdle in VATS thymectomy, specially in larger tumors. For that, some authors suggest retracting the sternum using a 10 mm cotton string caught on the stainless steel rod at the head of the table and tied to the hook of a Kent retractor at the thigh level [10]. Because of the age of the Human cadaver, we could not identify any thymus tissue. The average size of the resected thymus in patients with thymoma is bigger than the one of our study in porcine model. On one hand, identification of the limits of a large thymus is easier than a small one mixed with the surrounding fat. On the other hand, manipulating and dissecting 'healthy' thymus might be easier than pathologic, infiltrating ones.

Survival experiments were essential to prove that transesophageal HET was feasible and reliable. The cadaveric experiment proved that technically HET might be translated to humans. We believe that in the future HET could be regarded as an alternative to classic thoracoscopic approach for patients requiring thymectomy.

[References]

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[Tables]

Table I. Results of 4 acute and 8 survival experiments .

Experiment	Esophagotomy: min, complications	Thymus dissection and retrieval: min, complications	Closure: min, complications	Acute vs Survival
1	10	43	--	Acute
2	12	48 Small tear in the contralateral mediastinal pleura	--	Acute
3	15	35 3 Small tears in the pericardium	--	Acute
4	10	50	--	Acute
5	14	36 Small tear in the pericardium	15	Survival
6	15	50 Small tear in the pericardium	10	Survival
7	15	25 Small tear in the pericardium	5	Survival
8	18	19 Small tear in the contralateral mediastinal pleura	8	Survival
9	10	38 Small tear in the contralateral mediastinal pleura	12	Survival
10	15	35 Small tear in the contralateral mediastinal pleura	10	Survival
11	12	28 Small tear in the pericardium Partial resection of contralateral mediastinal pleura	5	Survival
12	8	17	5	Survival

[Figures]

Figure 1. Steps for hybrid endoscopic thymectomy (animal model). In A and B, main image represents thoracoscopic view, and insets represent gastrocopic view. In C and D, just gastroscopic image is represented. A, Gastroscope going through the submucosal tunnel and thoracoscope showing the exact site for esophagotomy, between the left phrenic nerve (p), the left costocervical vein (c), and the left subclavian artery (s). B, Dissection of the thymus (t) using a rigid dissector introduced through the thoracoscope working channel and conter-traction using a flexible grasper introduced through the gastroscope. One can see the counter-lateral lung (l) and the heart (h). C, A flexible grasper through the gastroscope introduces the specimens inside the endoscopic bag introduced through the transthoracic trocar. D, Closing the mucosal incision of the esophagus with 5 hemoclips.

Figure 2. Two specimens retrieved using an endoscopic bag from two consecutive experiments (animal model).

Figure 3. Micrographs of thymic specimens of the pig (haematoxylin and eosin stain). A, 4x Magnification: C – capsule; Cx – cortex; M – medulla; S – septum. B, 20x Magnification: H – Hassall corpuscle.

Figure 4. Gastroscopic image on the 14th postoperative day of experiment 8 (animal model) showing 2 esophageal hemoclips in place.

Figure 5. Thoracoscopic image on the 14th postoperative day of experiment 12 (animal model) showing the thoracotomy site (T) after dissecting local adhesions and some pleural adhesions in the apex and next to the left subclavian artery (s).

Figure 6. Micrographs of esophageal specimens of the pig on the 14th postoperative day (Masson's thricrome stain). A, Site of mucosal incision: m - mucosa; sm – submucosa. B, Site of myotomy: M – outter muscle layer.

Figure 7. Thoracoscopic view (left side) of the human cadaver. A) Exact site for esophagotomy. B) Final view after anterior mediastinum dissection

[Videos]

Video 1. Transesophageal access creation. Main image represents thoracoscopic view, and inset represents gastrocopic view. An operative thoracoscope with a 5-mm working channel was introduced through an 11-mm trocar inserted in the 2nd intercostal space in the left anterior axillary line. A forward-viewing, single-channel gastroscope was advanced into the esophagus, identifying the position of the thoracoscope and determining the esophagotomy site. 5 mL of saline solution was injected into the submucosa, 8 cm proximal to the esophagotomy position. An 1-cm longitudinal incision was made in the mucosa using an endoscopic needle-knife. Then, an 8- to 9-cm long submucosal tunnel was created by blunt dissection. While the submucosal tunnel was being created in the esophagus, the left mediastinal pleura was opened and the left posterior limits of the thymus dissected using rigid instruments introduced through the transthoracic trocar.

Video 2. Thymus dissection. Main image represents thoracoscopic view, and inset represents gastrocopic view. Dissection of the thymus was completed using both flexible (gastroscope) instruments and rigid (thoracoscope) intruments. The vessels were ligated using electrocautery alone, connected through the coagulation grasper introduced through the gastroscope or the rigid dissector entering through the thoracoscope working channel.

Video 3. Specimens retrieval. Image represents gastroscopic view. The thymus was retrieved through an endoscopic bag introduced through the transthoracic trocar. For that, the surgeon handling the gastroscope had to grasp the specimens and put it inside the endoscopic bag.

Video 4. Esophageal closure. Image represents gastroscopic view. The esophageal mucosa was closed at the proximal edge of the submucosal tunnel by using 4 to 5 flexible hemoclips.

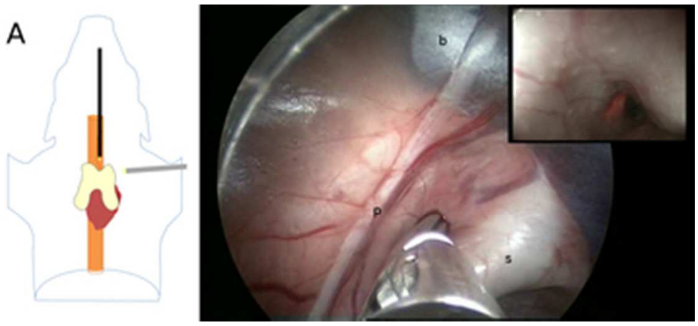

Figure 1. Steps for hybrid endoscopic thymectomy (animal model). In A and B, main image represents thoracoscopic view, and insets represent gastrocopic view. In C and D, just gastroscopic image is represented. A, Gastroscope going through the submucosal tunnel and thoracoscope showing the exact site for esophagotomy, between the left phrenic nerve (p), the left costocervical vein (c), and the left subclavian artery (s).
15x6mm (600 x 600 DPI)

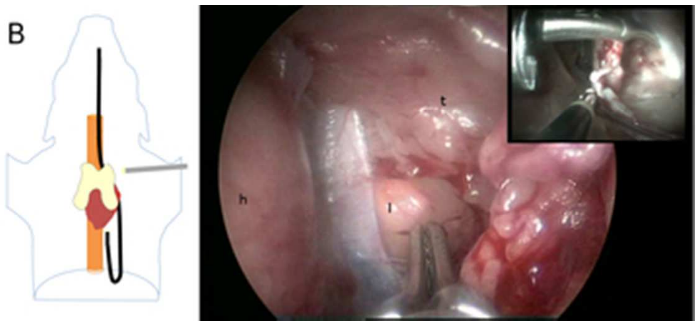

Figure 1. B, Dissection of the thymus (t) using a rigid dissector introduced through the thoracoscope working channel and conter-traction using a flexible grasper introduced through the gastroscope. One can see the counter-lateral lung (l) and the heart (h).
15x6mm (600 x 600 DPI)

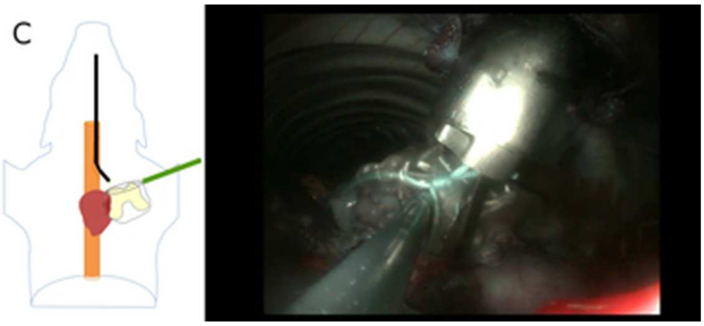

Figure 1C, A flexible grasper through the gastroscope introduces the specimens inside the endoscopic bag introduced through the transthoracic trocar.
15x6mm (600 x 600 DPI)

Figure 1D, Closing the mucosal incision of the esophagus with 5 hemoclips.
15x6mm (600 x 600 DPI)

Figure 2. Two specimens retrieved using an endoscopic bag from two consecutive experiments (animal model).
10x6mm (600 x 600 DPI)

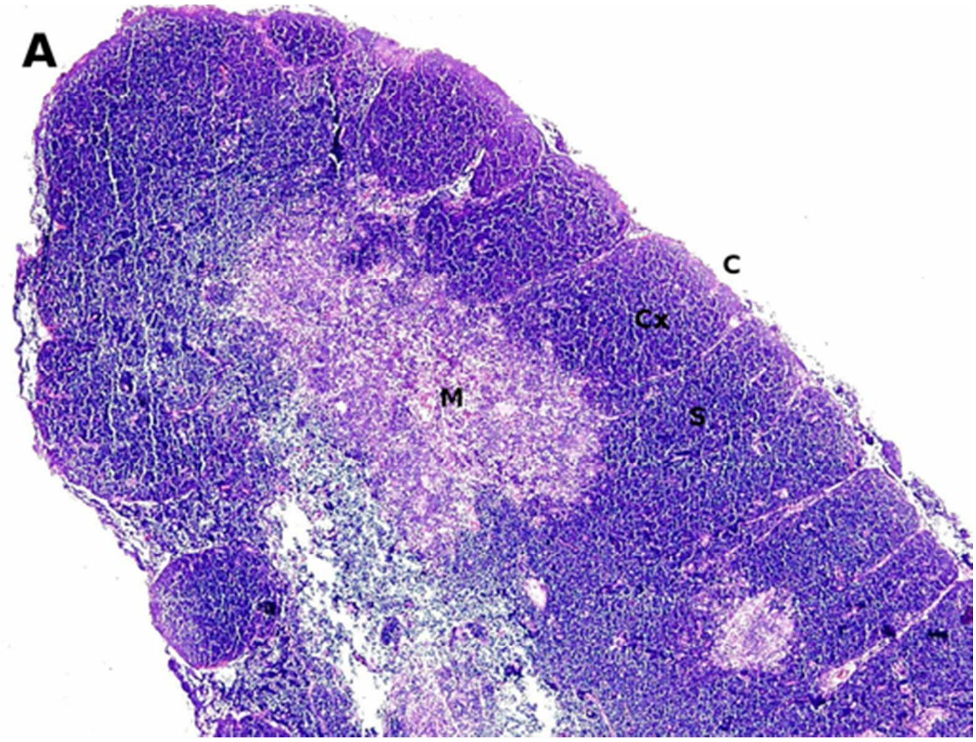

Figure 3. Micrographs of thymic specimens of the pig (haematoxylin and eosin stain). A, 4x Magnification: C – capsule; Cx – cortex; M – medulla; S – septum.
21x16mm (600 x 600 DPI)

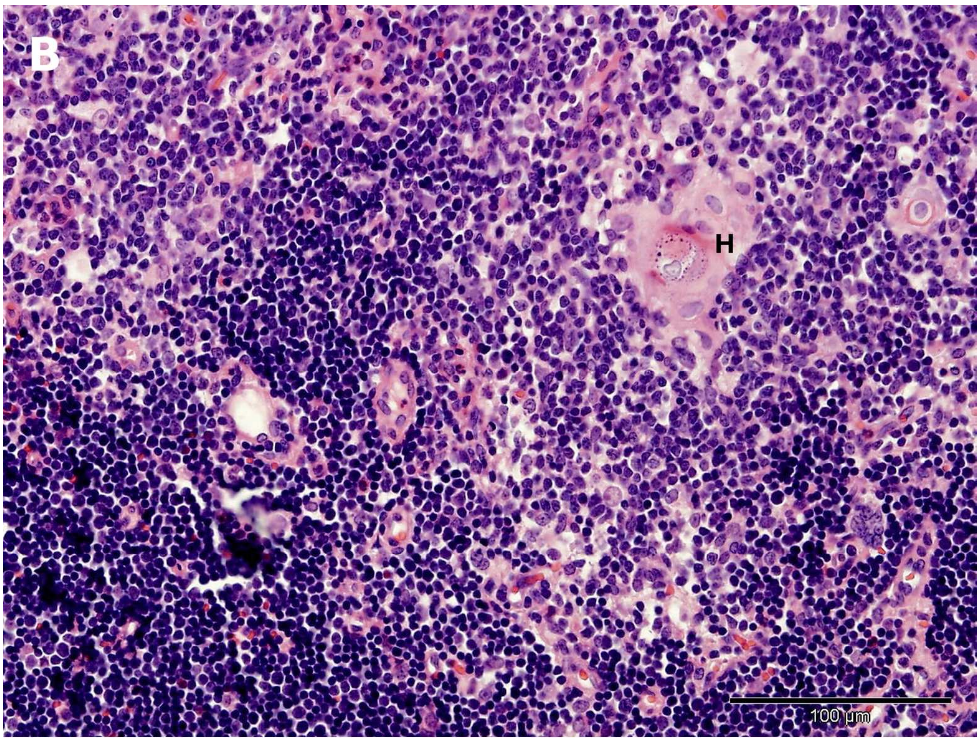

Figure 3B, 20x Magnification: H – Hassall corpuscle.
230x173mm (150 x 150 DPI)

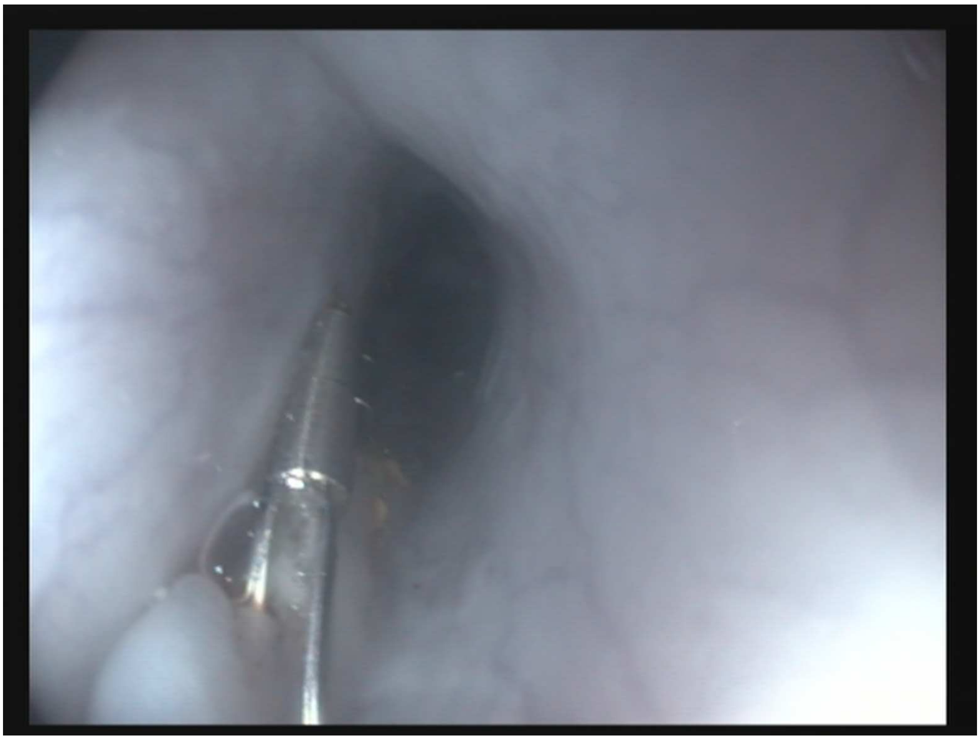

Figure 4. Gastroscopic image on the 14th postoperative day of experiment 8 (animal model) showing 2 esophageal hemoclips in place.
361x270mm (72 x 72 DPI)

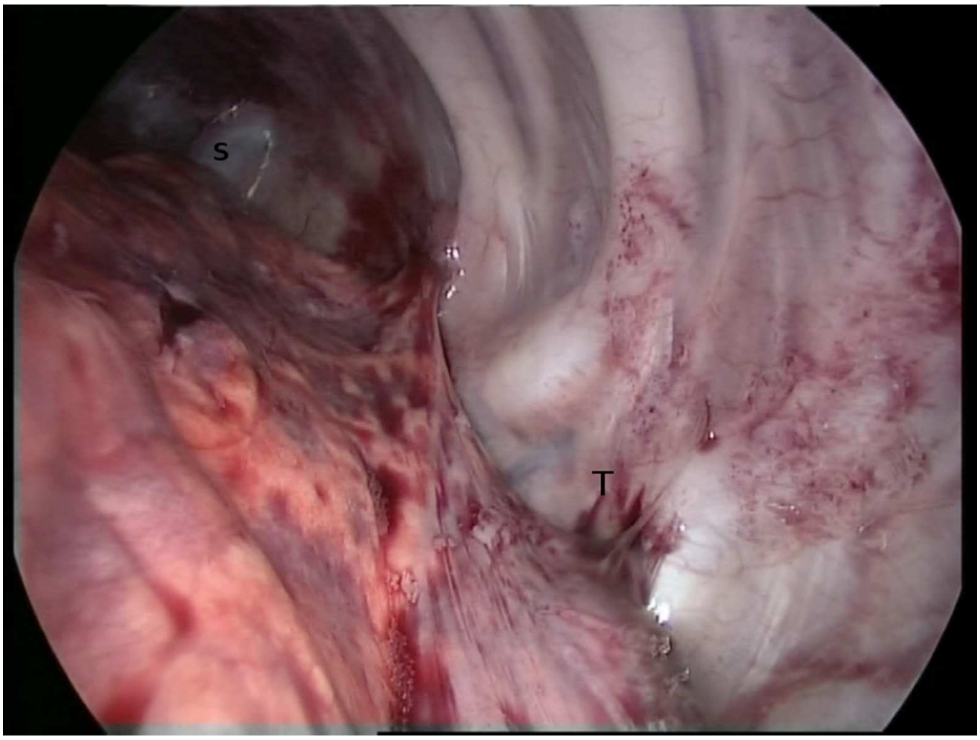

Figure 5. Thoracoscopic image on the 14th postoperative day of experiment 12 (animal model) showing the thoracotomy site (T) after dissecting local adhesions and some pleural adhesions in the apex and next to the left subclavian artery (s).
270x203mm (72 x 72 DPI)

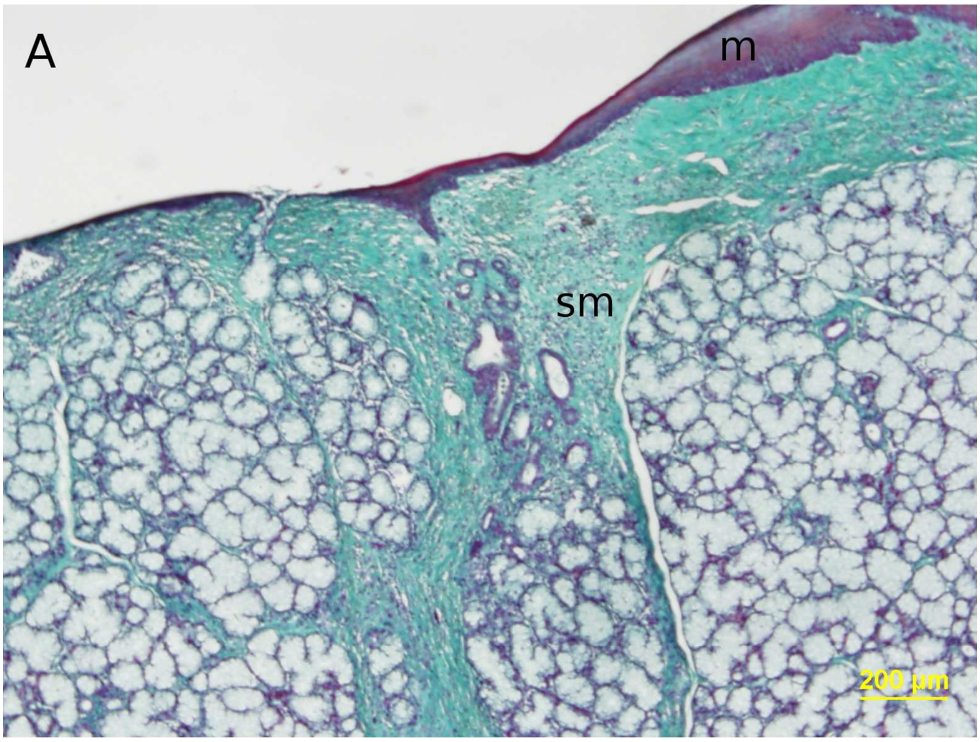

Figure 6. Micrographs of esophageal specimens of the pig on the 14th postoperative day (Masson's thricrome stain). A, Site of mucosal incision: m - mucosa; sm – submucosa.
479x361mm (72 x 72 DPI)

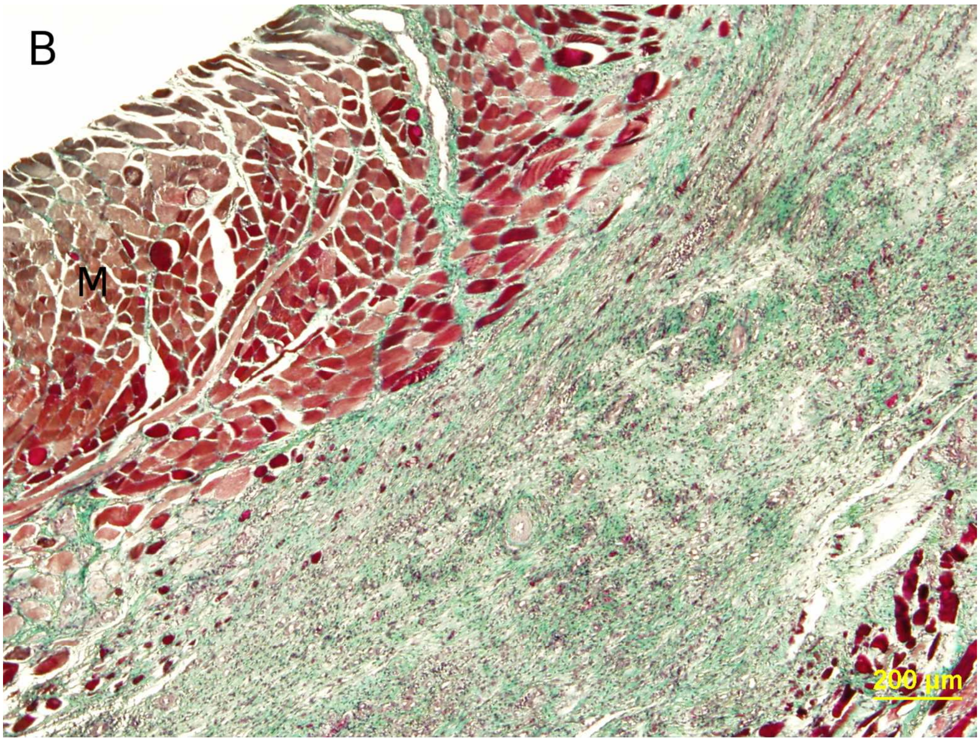

Figure 6B, Site of myotomy: M – outter muscle layer.
479x361mm (72 x 72 DPI)

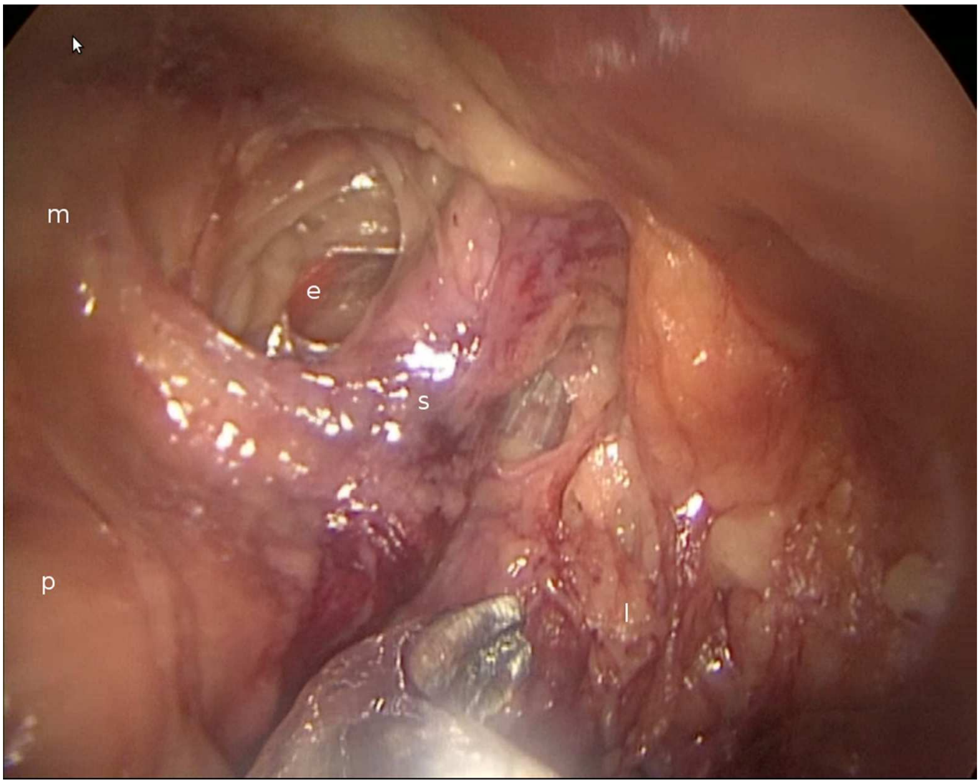

Figure 7. Exact site for esophagotomy. Thoracoscopic view (left side) of the human cadaver: esophagus (e), subclavian artery (s), anterior mediastinum (m), pericardium (p), lung (l).
350x279mm (72 x 72 DPI)

Chapter 5 | DISCUSSION

5. Discussion

Recent achievements in NOTES has permitted the evolution of the different natural orifices approaches themselves. The performance of endoscopic submucosal transesophageal myotomy is a perfect example of this. Pasricha *et al*. used submucosal endoscopy with mucosal flap (SEMF) to perform per-oral endoscopic myotomy (POEM) in an experimental setting (Pasricha *et al.*, 2007). Soon after this, Inoue *et al.* reported the first clinical experience of POEM for the treatment of achalasia (Inoue *et al.*, 2010). In 17 consecutive patients, there were no intraoperative or postoperative complications, and the occasions of inadvertent entry into the cardiac mucosa (2 patients) and the exposure of mediastinal tissue (4 patients) were without incident. Although POEM might not be considered a true NOTES procedure because it does not divide all the layers of the esophagus, it does use readily available endoscopic equipment and techniques and directly competes with a laparoscopic procedure (Makris *et al.*, 2010). We can say that NOTES experimental setting has permitted the evolution of endoscopic surgery as a whole and made gastroenterologists and surgeons question some dogmas, including concerns about esophagotomy closure, pneumothorax management and infection prevention. We wrote a review article on Natural Transesophageal Endoscopic Surgery (Annex 2).

5.1 Esophagotomy creation

When Sumyiama *et al.* presented transesophageal access to the thorax and mediastinum they described what they called submucosal endoscopy with mucosal flap (SEMF) (Sumyiama *et al.*, 2007). The authors injected saline into the esophageal submucosal layer creating a bleb and high-pressure CO_2 was used to perform a submucosal dissection. A biliary retrieval balloon was then inserted into the submucosal layer and was distended to enlarge the mucosal hole and create a 10-

cm long submucosal tunnel. Then, they used an endoscopic mucosal resection (EMR) cap (Olympus, Tokyo, Japan) to create a defect in the muscularis propria and the mediastinum was entered. The key of the method is the overlying mucosa which serves as a sealant flap minimizing the risk of soiling a body cavity with luminal contents and the ease by which the entry point into the submucosal working space can be closed (Sumyiama *et al.*, 2011).

With or without submucosal tunneling, transesophageal approach to the thoracic cavity is highly risky because of possible mechanical abrasion and trauma to surrounding structures (Sumyiama *et al.*, 2008; Von Rentein *et al.*, 2011). As stated in Introduction section, Fritscher-Ravens *et al.* proposed EUS-assisted transesophageal access. As an alternative, Rolanda *et al.* suggested single transthoracic port assistance for transesophageal NOTES (Rolanda *et al.*, 2008).

As we demonstrated in our experiments, using a 12 mm incision and the introduction of a 10 mm port, one can perform safe esophagotomy. We can also introduce flexible and rigid triangulating instruments for secure tissue manipulation, dissection and suture. Moreover, the trans-thoracic port can be used to create and control the pressure of pneumothorax. In the end of the procedure, the trans-thoracic port is used to insert a thoracic tube for postoperative drainage.

5.2 Esophagotomy closure

When SEMF is used to create transesophageal access esophagotomy closure is made easier as the overlying mucosa serves as a sealant flap. Most authors use endoclips to close the defect of the mucosa, but in the early studies the mucosa was left open with good clinical outcomes. Turner *et al.* published a study comparing esophageal submucosal tunnel closure with a stent versus no closure (Turner *et al.*, 2011). In this study, the unstented group achieved endoscopic and histological evidence of complete re-epithelialization and healing (100%) at the mucosectomy site compared with the stented group (20%, P = .048). So, it seems that the placement of a covered esophageal stent prejudices healing of the mucosectomy site.

When direct incision esophagotomy is performed a full-thickness healing of the mucosal and muscular layer must be achieved. Fritscher-Raves *et al.* compared endoscopic clip-closure (ECC) versus endoscopic suturing versus thoracoscopic repair of a 2-2.5 cm esophageal incision (Fritscher-Raves *et al.*, 2010). Endoscopic suturing was achieved using a prototype suturing system that deploys a metal anchor with a nonabsorbable oplypropylene thread (T-bar) on each side of the esophageal defect (CR Bard, Murray Hill, NJ; Ethicon Endosurgery, Cincinnati, Ohio, USA). The two threads were joined together using a small cylindrical suture-locking device, approximating both sides of the incision. Three to 5 pairs of T-bars were used to close the defect. Thoracoscopic repair took the longest time because of port placement and dissection of the peri-esophageal tissue for localization of the defect in the esophagus. Although ECC was the fastest technique, it could not achieve full-thickness repair of the esophageal wall. Moreover, larger gaping defects could not be bridged by the jaws of the clips. In contrast, ECS anchors were deployed across the entire esophageal wall and showed well-healed scares with the smallest remaining gaps. On of the disadvantages of T-bars is that placing them beyond the gastrointestinal wall cannot be performed under direct vision. So, the needle tip may harm or inadvertently place a T-bar into an unwanted structure as reported in a previous study (Raju *et al.*, 2008).

The over-the-scope clip (OTSC) system showed promising results for gastrostomy closure (Rolanda *et* al., 2009). It has also been used in for closure of postoperative leaks following gastrectomy and primary repair after spontaneous acute esophageal perforation (Pohl *et al.*, 2010). Cardiac septal occluders might be a valuable alternative. Repici *et al.* have reported the first human case of esophagus-tracheal fistula closure by using a cardiac septal occluder with good results (Repici *et al.*, 2010). Other prototype suturing/apposition devices might be of future use in esophagotomy closure, namely Padlock-G clips (Aponos Medical, Kingston, New Hampshire, USA), NDO Plicator (NDO Surgical Inc., Mansfield, Massachusetts, USA), g-Cath/g-Prox (Usgi Medical Inc, San Clemente, California, USA), flexible Endostich (Covidien, North Haven, Conneticut, USA), OverStich (Apollo Endosurgery, Austin, Texas, USA), Direct Drive Endoscopic System (DDES Boston Scientific, Natick, Massachusetts, USA), Anubis-scope (Karl Storz, Tuttlingen, Germany) and Endo-Samurai (Olympus, Tokyo, Japan) (Desilets *et al.*, 2010; McGee *et al.*, 2008; Seaman *et al.*, 2006; Voermans *et al.*, 2008; Kantsevoy and Thuluvath, 2012; Thompson *et al.*, 2009; Dallemagne and Marescaux, 2010; Spaun *et al.*, 2009).

Von Reitein *et al.* presented a prototype self-expanding metal stent (SX-ELLA stent, ELLA-CS, Hradec Kralove, Czech Republic) for direct incision esophagotomy closure without any suture (Von Reitein *et al.*, 2010). Fifteen-millimeter direct incision esophagotomies were created in 12 domestic pigs using a prototype endoscopic Maryland dissector (Ethicon Endosurgery, Cincinnati, Ohio, USA). Six animals were randomly assigned to open surgical repair and six animals to endoscopic closure using the self-expanding, covered, nitinol stent in a non-survival setting. Pressurized leak test results were not different for stent compared to surgical closures. Six animals underwent transesophageal endoscopic mediastinal interventions and survived for 17 days. Stents were extracted at day 10. All survival animals were found to have complete closure and adequate healing of the esophagotomies, without leakage or infectious complications.

The hybrid thoracic NOTES presented by Rolanda *et al.* was useful for esophagotomy closure. Using a thoracoscope with a 5mm working channel, the authors inserted a needle-holder and performed an end-to-end esophageal anastomosis with gastroscopic instruments assistance (Rolanda *et al.*, 2011). In our first study, the hybrid approach permitted testing other alternative technique for esophagotomy closure using the SILS stitch™ (Covidien) introduced through the pig's mouth (Moreira-Pinto, 2012). All the movements of this suture device were guided by the image on the thoracoscope. Simultaneously, the insertion of the grasper through the thoracoscope’s working channel aided the positioning of the esophagus wall margin within the device’s jaws. In this way, we managed to get a full-thickness wall suture of the esophagus An esophageal stent was left in place. Although no leakage was found at the end of the procedure, endoscopic examination in the 15 postoperative day revealed a pseudo-diverticulum in one animal, and wound dehiscence with confined collection/recess in the remaining three animals. As no specimen was to be retrieved through the esophagus in the LAA ligation and the thymetcomy protocols, SEMF was used to enter the thorax (Moreira-Pinto, 2012). In the end of the preocedures, esophageal mucosa defect was closed using endoscopic clips. Excellent results were achieved with this technique as endoscopic and thoracoscopic examination found complete healing of the mucosa and the muscularis of the esophagus by the 14 postoperative day in every pig.

In the later protocol, transesophageal access was created in the human cadaver. The SEMF was performed and myotomy at the end of the submucosal tunnel was performed with thoracoscopic visual control. The single transthoracic thoracoscope permitted determining the exact site for esophagotomy avoiding the lesion of vital organs around the esophagus.

5.3 Mediastinum and pneumothorax management

Injecting air or CO_2 is a key component for adequate exposure and visualization, especially in thoracic NOTES. Air inflated in an uncontrolled manner through the endoscope results in wide fluctuations in intrathoracic pressures, over-distension of the gastrointestinal tract and adverse hemodynamic effects. Von Delius *et al.* studied the potential cardiopulmonary effects of transesophageal mediastinoscopy in a porcine model, using a conventional gastroscope (Von Delius *et al.*, 2010). Air inflation was manually performed and the pressure was monitored through the working port of the gastroscope. In 3 of the 8 pigs, there was pleural injury with tension pneumothorax, resulting in hemodynamic instability. In the remaining 5 pigs, median mediastinal pressure maintained was 4.5 mmHg (mean 5.4 +/- 2.2 mmHg). In this uncomplicated mediastinoscopies, peak inspiratory pressures, pH, partial pressure of CO_2, and partial pressure of oxygen (O_2) were not influenced.

Inadvertent high pressure pneumomediastinum and pneumothorax have been major complications since the beginning of thoracic NOTES. Most authors use thoracic tube drainage for pressure relief. As CO_2 pressure control is also a main concern in abdominal endoscopic surgery, new insufflators have been adapted to both deliver and monitor CO_2 through the endoscope (Park *et al.* 2007). These may be of some use in transesophageal NOTES. Meanwhile, using a Veress needle or a transthoracic port may be a secure way to achieve good pneumothorax pressure control.

There is a great debate whether CO_2 or room air should be used for transesophageal NOTES. CO_2 is far more soluble in blood than air and fatal CO_2 embolism is rare. The effect of CO_2 with respect to laparoscopy has suggested an overall attenuated inflammatory response that may provide a further immunologic benefit. Conversely, room air laparoscopy has been shown to generate a greater inflammatory response, but a recent case-control study did not find a significant difference between the peritoneal inflammatory response of NOTES versus laparoscopy with CO_2 and air pneumoperitoneum (Trunzo *et al.*, 2010).

Even for intra-esophageal endoscopic surgery, the question if either air or CO_2-insufflation should be used is relevant. A study from Uemura *et al.* found a decreased need for midazolam in patients undergoing esophageal endoscopic submucosal dissection with CO_2-insufflation when compared to air-inflation. The authors attributed this decreased need for midazolam to decreased procedural pain (Uemura *et al.*, 2012). In human POEM procedures, only CO_2-insufflation has been used (Swanström *et al.*, 2011). Inoue *et al.* reported that none of the 17 patients in their series had postoperative subcutaneous emphysema, but CT scan just after procedure revealed a small amount of CO_2 deposition in the peri-esophageal mediastinum. The authors suggest that positive pressure ventilation with endotracheal intubation should be maintained at higher pressures than those generated by endoscopic CO_2-insufflation in order to reduce mediastinal emphysema but also to reduce the risk of air embolism (Inoue *et al.*, 2010).

In their series of 5 patients undergoing POEM, Swaanström *et al.* observed the development of pneumoperitoneum in 3 patients and placement of a Veress needle was necessary to decompress it (Swanström *et al.*, 2011). According to the authors, Inoue described this occurrence as well in 10% of this most recent series of more than 100 patients (personal communication) and theorized that it might occur due to gas permeation through the remarkably thin longitudinal muscle fibers of the esophagus.

One of the major advantages of hybrid thoracic NOTES is permitting both a good pneumothorax control during the thoracoscopic procedure connecting a CO_2-insufflator the the transthoracic port and a effective postoperative drainage of the thorax using a tube inserted through the transthoracic incision (Moreira-Pinto, 2011). This is important because the gastroscope keeps inflating room air as well as saline solution through all the procedure. Infalting CO_2 though the transthoracic port dilutes the O_2 inside the thorax, diminishing the risk of explosion and gas embolism. In the end of our procedures, a tube was placed through the thoracic incision to drain all the gas and liquid acutely. That was enough for all our survival assessments.

5.4 Infection prevention

Since the beginning of NOTES, sterility has been a hurdle. Infection must be prevented by using a clean access site. Most transesophageal protocols follow a 12-24 hour liquid formula diet, intravenous antibiotics and esophageal and stomach irrigation with saline or iodopuvidone solution. Despite these precautions, even a sterile overtube used to protect the endoscope from oral contamination becomes contaminated on oral insertion and can transport bacteria to the esophagus, the mediastinum and the thorax. Several infectious complications have been reported. In a study by Fritscher-Ravens *et al.* two out of 12 pigs had reflux of gastric contents into the esophagus that resulted in spillage through the esophagotomy (Fritscher-Ravens *et al.*, 2010). The study protocol included 12-hour fasting period before surgery and a 3-day antibiotherapy with enrofloxacin. Despite this, one animal died of severe mediastinitis, whereas the other one developed a subclinical mediastinal abscess found on necropsy. The authors suggested that careful aspiration of gastric contents at the beginning of the procedure should always be performed. Also, the authors concluded that 12 hours of fasting may be too short a time to clear the stomach of the animals well enough. In a previous study by Gee *et al.* one out of four animals developed submucosal abscess, despite 24-hour liquid diet, esophagus and stomach lavage with iodopuvidone solution and cefazolin injection preoperatively (Gee *et al.*, 2008).

There is also some controversy about the need for endoscope sterilization. In a literature review, Spaun *et al.* concluded that, although difficult, it is possible to terminally sterilize flexible endoscopes. Steris System that uses 0.2% peracetic acid was the cheapest and fastest sterilization method and scored second in the risk of recontamination. Ethylene oxide gas sterilization has the lowest risk of recontamination, but is the slowest and most expensive method. The authors recommend sterile instrumentation for clinical NOTES until well-designed and randomized clinical trials are available and guidelines are published (Spaun *et al.*, 2010).

When transferring the results from animal experiments to human settings, one should keep in mind that anatomy and physiology of the esophagus and the mediastinum in humans are somewhat different from those of the pig, especially with regard to wall structure, motility and infection pathophysiology of the mediastinum. In humans, a perforation of the esophagus causes severe complications or even death in at least 30-50% of cases (Grund and Lehmann, 2010). In human POEM, patients are placed on a clear liquid diet 24 hours and given a single preoperative dose of a first generation cefalosporin. Although published series account for a short number of patients, no infectious complications were reported. Neither studies specify if the flexible endoscope was either completely sterilized or conventionally disinfected.

In our survival series, non-sterile flexible endoscopes and endoscopic instruments were used.

Antibiotic ceftiofur hydrochloride (5 mg/kg, IM) was given preoperatively and repeated at 24-hour intervals for three consecutive days. That was enough to prevent thoracic infection in all animals (Moreira-Pinto, 2012).

5.5 Complex thoracoscopic procedures

In hybrid thoracic NOTES we are combing transesophageal endoscopy with single transthoracic port assistance. That means we have two different entry sites into the thoracic cavity. Combining them, we can obtain regular triangulation and counter-traction, mimicking the two hand movements of the surgeon and promoting secure manipulation of tissues, careful dissection and effective electrocoagulation. The flexible endoscope inside the thorax allows looking all over the cavity, including sites where rigid transthoracic endoscopes can not reach – namely the ipsilateral chest wall, the diaphragm and the counterlateral thoracic cavity. Moreover, one can both guide instruments introduced through the esophagus by transthoracic visualization (staplers, SILS stitch, knot-pusher) and guide instruments introduced through the transthoracic port by gastroscopic visualization (grasper, endoscopic bag). These possibilities of hybrid thoracic NOTES permits moving towards more complex thoracoscopic procedures.

Some may find that, the introduction of a transthoracic port is a step back in the path of scarless surgery. Pulmonary lobectomy, LAA ligation and thymectomy would be very difficult to perform using a single flexible gastroscope with instruments entering in a parallel fashion. A single transthoracic port gives new possibilities to NOTES, making it more reliable and safer. In fact, during our protocols, single transthoracic port proved its value by permitting a safe and more accurate esophagotomy creation, enabling a better pneumothorax pressure control and postoperative drainage, and therefore allowing complex thoracoscopic procedures.

Correction of esophageal atresia implies esophagotomy of the proximal pouch and end-to-end anastomosis with the distal portion of the esophagus. It is a highly complex procedure that must be performed during the first days of life. Surgeons have been trying different ways of using the esophagotomy site to avoid further thoracic incisions. In 2011, Ishimaru *et al.* published a pilot study of laparoscopic gastric pull-up by using NOTES for treating long-gap esophageal atresia. The procedure included (1) creation of the disease model by laparoscopic resection of the lower esophagus, (2) laparoscopic fundoplication, complete mobilization of the stomach, and enlargement of the esophageal hiatus, (3) formation of a per-oral transesophageal entry site into either the posterior mediastinum or the right thoracic cavity followed by fashioning a tunnel to the peritoneal cavity, (4) gastric pull-up by using both laparoscopy and NOTES, (5) esophagoesophageal anastomosis using a prototype of the double T-bar suturing device. Nonsurvival experiments were conducted in 9 pigs. Two disorientations and one hemorrhagic death occurred during step three (Ishimaru *et al.*, 2011). The same group presented a complete transluminal esophageal anastomosis as follows: a BraceBar™ (Olympus Medical Systems Corp., Tokyo, Japan), which is a double T-bar suturing device, was placed endoscopically at the blind end of the upper esophagus (UE); (2) the blind end was incised, and the scope was advanced out of the esophagus; (3) a balloon catheter was inserted into the lower esophagus (LE); (4) the catheter and a thread on the BraceBar were withdrawn so that the end of the UE was inverted, and the LE was pulled into the UE; (5) after the catheter was removed, a short tube was placed inside the duplicated part of the esophagus via the transgastric route; (6) a double ligature was performed using a ligating device over the tube. The authors performed this procedure in eight *ex-vivo* porcine models. All steps in this procedure were technically successful under the endoscopic visualization without any assistance from outside of the esophagus (Ishimaru *et al.*, 2012).

Having hybrid thoracic NOTES in mind, our group suggested esophagoesophageal anastomosis with single transthoracic port assistance in the rabbit model (Henriques-Coelho *et al.*, 2012). We combined transesophageal access with a single transthoracic port combined with a per-oral access to simulate repair of esophageal atresia in a human newborn. We used a transthoracic telescope with a 3-mm working channel, a flexible endoscope with a 2.2-mm working channel by per-oral access, and combined transthoracic and per-oral 3-mm instruments (Annex 3). Again, we believe that translating thoracic NOTES to humans will be safer and easier if we have the visual control and the rigid instruments provided by the single transthoracic port.

Chapter 6 | CONCLUSIONS

6. Conclusions

Transesophageal NOTES offers new possibilities in less invasive access to mediastinal and thoracic cavities. Ongoing NOTES revolution permitted the development of esophageal submucosal endoscopic techniques with almost immediate human application. POEM is a perfect example of this. Theoretical advantages of transesophageal NOTES warrant the continuation of research, although some hurdles are to be overcome. The critical nature of the organs that involve the esophagus, the risk of hemodynamic instability related to pressure pneumomediastinum and pneumothorax and potential infectious complications call for caution when transition to human practice. Looking at the sudden widespread of POEM, the human translation of NOTES may not take long. In this thesis, we present hybrid thoracic NOTES as the key to perform this translation as safe as possible.

Hybrid thoracic NOTES gives visual control of transesophageal access creation, permits triangulation and counter-traction using flexible instruments inserted through the gastroscope and rigid instruments inserted through the thoracoscope, and offers a good intra-thoracic pressure control and pneumothorax drainage. Hybrid thoracic NOTES permits performing highly complex thoracoscopic procedures. Some may question if we are doing single-port thoracoscopic surgery with per-oral (transesophageal) assistance and not transesophageal endoscopic surgery with minor transthoracic assistance. Nomenclature should not be a problem. In fact, NOTES (hybrid or pure) or even scarless surgery should not be an obsession for physicians. The main goal for physicians should be minimally invasiveness, meaning to cure doing the least harm as possible. This should be done with the knowledge and technology we have today. Today we have lots of limitations when trying to use flexible gastroscopes and their instruments alone to perform complex thoracoscopic procedures. In the future, advances in endoscopic instruments might dismiss the use of any transthoracic assistance, but for the time being hybrid approach seems the safest and least invasiveness way to do it. It might seem that we are stepping back to classical thoracoscopy, but we are actually improving it with knowledge taken from this NOTES journey.

Chapter 7 | REFERENCES

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ANNEXES

Annex 1. Natural orifice transluminal endoscopy surgery

Moreira-Pinto J, Lima E, Correia-Pinto J, Rolanda C. Natural orifice transluminal endoscopy surgery: A review. World J Gastroenterol 2011; 17: 3795-3801.

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i33.3795

World J Gastroenterol 2011 September 7; 17(33): 3795-3801
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Natural orifice transluminal endoscopy surgery: A review

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Received: October 4, 2010 **Revised:** December 1, 2010
Accepted: December 8, 2010
Published online: September 7, 2011

Abstract

Minimally invasive surgery started spreading worldwide in 1987, when the first laparoscopic cholecystectomy was performed. Meanwhile, improvement of endoscopic equipment and instruments allowed gastroenterologists to attempt more aggressive endoluminal interventions, even beyond the wall barrier. The first transgastric peritoneoscopy, in 2004, brought to light the concept of natural orifice transluminal endoscopic surgery (NOTES). The idea of incisionless surgery is attractive and has become a new goal for both surgeons and other people interested in this field of investigation. The authors present a review of all developments concerning NOTES, including animal studies and human experience.

Key words: Transesophageal; Transgastric; Transvesical; Transvaginal; Transcolonic; Natural orifice transluminal endoscopic surgery; Minimally invasive techniques

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Moreira-Pinto J, Lima E, Correia-Pinto J, Rolanda C. Natural orifice transluminal endoscopy surgery: A review. *World J Gastroenterol* 2011; 17(33): 3795-3801 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i33/3795.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i33.3795

INTRODUCTION

Surgery has experienced a huge development in the past three decades after Dr. Philippe Mouret performed the first laparoscopic cholecystectomy in 1987. Since then, minimally invasive surgery has begun to spread worldwide[1]. This was largely in part due to patient demands for laparoscopic surgery's advantages - shorter hospital stays, less pain, and smaller, less disfiguring scars[2]. The improvement of available equipment and instruments allowed more and more surgical procedures to be made through a minimally invasive approach, rapidly becoming a standard practice in most procedures.

At the same time, progresses in gastrointestinal endoscopy have made it an indispensable and multifaceted instrument for diagnosis and therapy. Besides endoluminal procedures, gastroenterologists attempted some interventions beyond the wall barrier, such as pseudocyst drainage[3] and percutaneous endoscopic gastrostomy[4]. However, it was not until 2004 that Kalloo *et al*[5] published the first report of a true transluminal procedure, a transgastric peritoneoscopy in a porcine model, which brought to light the concept of natural orifice transluminal endoscopic surgery (NOTES). The idea of incisionless surgery was attractive and has now become a new goal for both surgeons and other people interested in this field of investigation.

The term NOTES describes novel endoscopic interventions on internal organs performed through natural orifices[6]. In this new approach, endoscopes enter the abdominal and thoracic cavities *via* any single or combination of natural orifices - mouth, urethra, vagina, and anus. Depending on the orifice, rigid or flexible equipment can be used. The lower "short-ways" (bladder, colon or vagina) allow the easy passage of rigid or flexible instruments into the abdominal cavity, but the upper "long-ways" (esophagus and stomach) require flexible equipment[7] (Figure 1).

The main goal for NOTES is avoiding skin incisions. Other theoretical advantages include: decreased post-operative pain, reduction/elimination of general anesthesia, performance of procedures in an outpatient or even office setting, and possibly cost reduction. Moreover, eliminating skin incision avoids associated complications such as wound infections and hernias, as well as reduction in hospital stay, faster return to bowel function, improved cosmetic outcomes, and increased overall patient satisfaction[2].

WHAT DID THE INVESTIGATION ACHIEVE SO FAR?

The first challenge in NOTES is getting good and clean access to the cavity we want to "scope" (Table 1). The first mention of natural orifice procedure dates back to the 1940s, when culdoscopies were performed using an endoscope passed through the recto-uterine pouch to view pelvic organs, as well as to perform sterilization procedures[8]. At that time, these procedures did not gain much popularity and were restricted to some gynecological procedures. Recently, however, they were recovered by NOTES development. In 2002, Gettman *et al*[9] published one pure transvaginal nephrectomy along a series of hybrid transvaginal nephrectomy in a porcine model.

Taking advantage of the great developments in gastrointestinal endoscopy, some pioneers began working on the transgastric approach to the abdominal cavity. The first published description of transgastric peritoneoscopy was in 2004 by Kalloo *et al*[5], in a porcine model. Since then, a number of successful transgastric procedures have been attempted and performed[10-20]. These initial studies also identified major limitations of the isolated transgastric approach, mainly in more complex procedures such as cholecystectomy, first described in 2005 by Park *et al*[21]. Lack of triangulation and platform stability were the main problems identified. Searching for solutions to these problems, researchers tried other ways of entering the abdominal cavity. Fong *et al*[22-24] published the first transcolonic peritoneoscopy followed by a series of transcolonic procedures. The access from below gives a good, direct view of the upper abdominal cavity. Having that in mind, Lima *et al*[25] published the first transvesical endoscopic peritoneoscopy. And subsequently our group used a combination of transgastric and transvesical approaches to solve the problem of triangulation, and managed to do a series of cholecystectomies and nephrectomies in porcine models[26,27].

To accomplish NOTES procedures in the thorax, Sumiyama *et al*[28] proposed the transesophageal access. Transvesical-transdiaphragmatic thoracoscopy[29], transgastric-transdiaphragmatic thoracoscopy[30], and transtracheal thoracoscopy[31] have been suggested as well. Although the transesophageal method has been preferred as a direct entry to the thorax and posterior mediastinum, this permitted several simple thoracic procedures in porcine models[32-38].

CURRENT CHALLENGES

Despite the enthusiasm for NOTES, there are still some hurdles to be overcome. The initial concern is the potential for intra-abdominal infection and spillage from the viscerotomy. Infection must first be prevented by using a clean access site. Most transgastric protocols also follow a 24 h liquid formula diet, intravenous antibiotics and stomach irrigation with sterile water and antibiotic solution. Despite these precautions, even a sterile overtube used to protect the endoscope from oral contamination becomes contaminated on oral insertion and can transport bacteria to both the stomach and the peritoneal cavity[2]. Surprisingly, Narula *et al*[39] reported no infections after gastrotomy in patients undergoing diagnostic transgastric peritoneoscopy without previous gastric decontamination. The authors considered that the same degree of contamination of the peritoneal cavity is expected as in any operation performed with an open viscus.

There is also some controversy about the need for endoscope sterilization. In a recent literature review, Spaun *et al*[40] concluded that, although difficult, it is possible to terminally sterilize flexible endoscopes. Steris System 1™ that uses 0.2% peracetic acid was the cheapest and fastest sterilization method and scored second in the risk of recontamination. Ethylene oxide gas sterilization has the lowest risk of recontamination, but is the slowest and most expensive method. The authors recommend sterile instrumentation for clinical NOTES until well-designed and randomized clinical trials are available and guidelines are published.

Concerning viscerotomy closure, gastrotomy has been the most studied and the methods under investigation could also be applied to the colon, esophagus or bladder, depending on the circumstances. Several methods have been proposed for stomach closure, including: conventional endoscopic clips, over-the-scope clip (OTSC) system, septal occluders, T-tags, T-bars for tissue opposing, as well as more complex suturing devices such as the Eagle Claw Ⅶ, NDO Plicator, USGI Endosurgical Operating System, and linear endoscopic staplers. Most of these devices still have limitations that need improving, but OTSC shows the most promising results[41]. More recently, the Padlock-G clip have been described as also showing promising results[42]. Colonic closure in animal studies has been performed using the

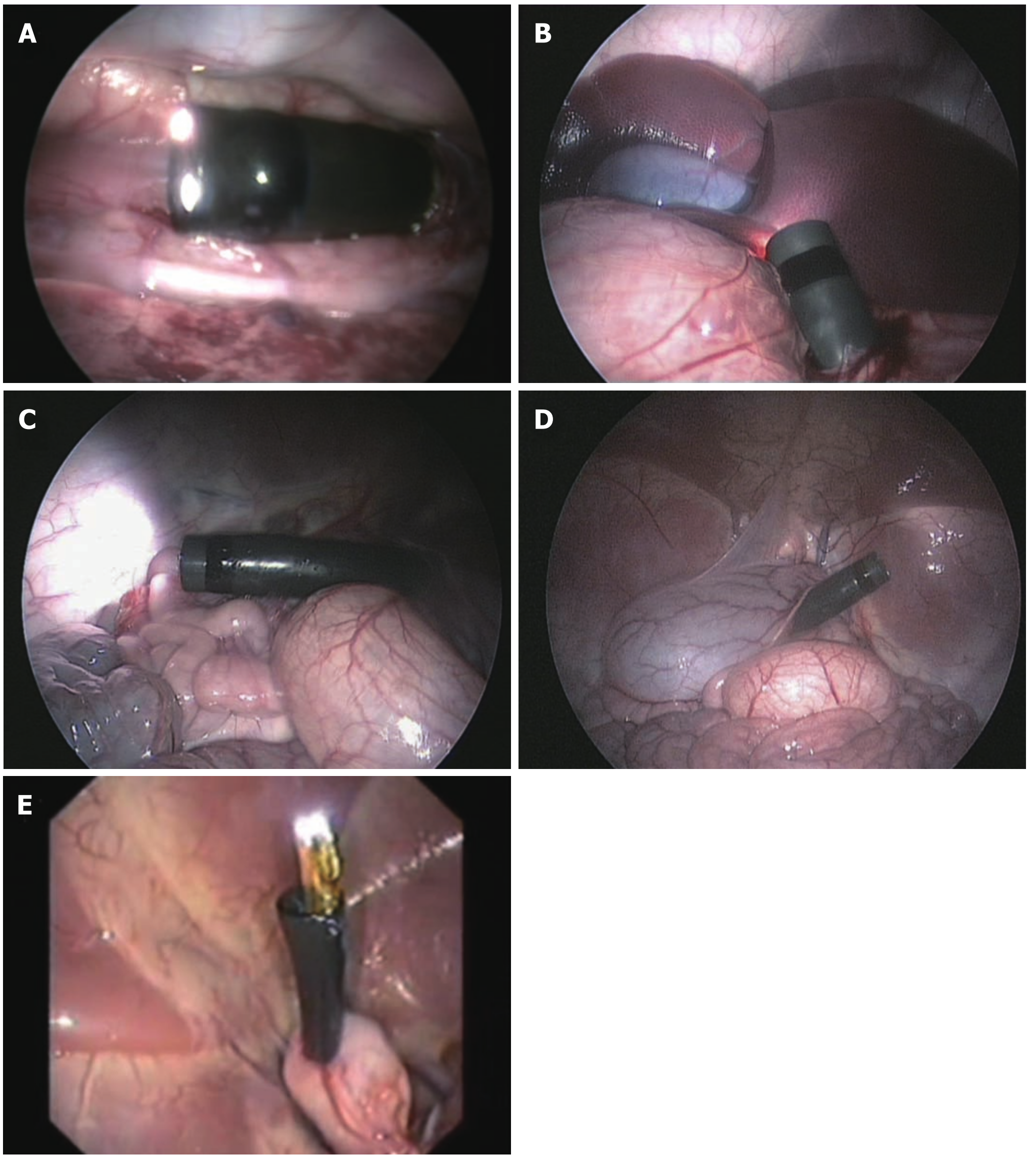

Figure 1 Internal view of natural orifice transluminal endoscopic surgery access (porcine model). A: Transthoracic view of transesophageal access; B: Transabdominal view of transgastric access; C: Transabdominal view of transcolonic access; D: Transabdominal view of transvaginal access; E: Transgastric view of transvesical access.

same techniques and devices as those used for gastrotomy closure. Transanal endoscopic microsurgery has been used for a long time, and has been useful for colonic closure in hybrid NOTES procedures in humans[43]. For vesicotomy closure, Lima *et al*[44] recently reported the first successful endoscopic closure using a suturing kit (T-fasteners with a locking clinch). Easy and safe closure has been the main advantage for transvaginal route acceptance. Closure after transvaginal access is readily and routinely performed by using standard surgical techniques. Even if closure were to fail, there would be little, if any, clinical significance, because of the extremely low risk of infection or hernia.

Concerning adequate exposure and visualization, pneumoperitoneum is a key component. Air insufflated in an uncontrolled manner through the endoscope results in wide fluctuations in intraperitoneal pressures, overdistension of the abdomen, and adverse hemodynamic effects. Insufflated air can also leak around the endoscope resulting in bowel overdistension[2]. Many authors are now using a Veress needle to inject carbon dioxide and safely control its pressure inside the abdomen[45]. Despite this, new insufflators are being adapted to both deliver and monitor carbon dioxide through the endoscope[46]. There is a great debate whether CO_2 or room air should be used. The effect of CO_2 with respect to laparoscopy has suggested an overall attenuated inflammatory response that may provide a further immunologic benefit. The acidic environment created has been the main contributing factor believed to facilitate this physiologic result. Conversely, "room air" laparoscopy has been shown to generate a greater inflammatory response, but a recent case-control study did not find a significant difference between the peritoneal inflammatory response of NOTES *vs* laparoscopy with carbon dioxide and air pneumoperitoneum[47].

As previously stated, maintaining spatial orientation and triangulation of instruments is challenging when using a flexible endoscope. Moreover, flexible endoscopes are difficult to stabilize inside the abdominal cavity and can only pass flexible instruments which are too flaccid for retraction. This challenge can be overcome with

Table 1 Major features of the different natural orifice transluminal endoscopic surgery access for thoracic and abdominal cavities

	Transesophageal	Transgastric	Transvesical	Transvaginal	Transcolonic
Rigid instruments	No	No	Yes	Yes	Yes
Available in both genders	Yes	Yes	Yes	No	Yes
Sterility	No	No	Yes	No	No
Size	Wide	Wide	Up to 6 mm	Wide	Wide
Closure	Endoscopic (in study)	Endoscopic (in study)	Endoscopic (in study)	Direct suture	Endoscopic (in study)
Specimen retrieval	Not reported	Possible	Not reported	Possible	Possible

adequate training, a combination of different routes, and with the constant development of new instruments. Transvaginal, transcolonic and transvesical routes allow the introduction of rigid equipment, and except in the transvesical route, the instruments can be used either through a rigid endoscope or in parallel with a flexible endoscope. Additionally, these access routes coming from the lower abdomen permit a good direct visualization of the upper abdomen. In some cases, one can use an additional transabdominal port. This has been named hybrid NOTES and has been seen as an intermediate step of great help in the training and development of NOTES[48]. Recently, magnets are being managed to provide the vigorous traction and countertraction required to advance NOTES procedures[49]. A new magnetic anchoring and guidance system allows concurrent use of multiple working instruments and control of an intra-abdominal camera. It has been used to perform transvaginal, single-port cholecystectomy[50]. Finally, one of the hurdles of NOTES is getting solid organs out of the thoracic and abdominal cavities. Excision of larger organs such as a kidney, or a gallbladder filled with stones through a small trocar orifice is a huge challenge. The transvaginal access has a big advantage in this matter and has been used for specimen retrieval in most NOTES procedures. On the other hand, transvaginal access is only an option in female patients.

HUMAN EXPERIENCE

In 2003, Rao and Reddy[51] performed the first NOTES procedure in humans. The authors carried out a transgastric appendectomy in a male patient presenting severe burn lesions in his abdominal wall using a conventional flexible endoscope with two working channels. Only in 2007, was there the first published human NOTES procedure. Marks *et al*[52] performed a transgastric rescue of a prematurely dislodge gastrostomy tube. The authors advanced a standard gastroscope through the previous gastrostomy, a performed peritoneoscopy, and suctioned away intra-abdominal free fluid. In that same year, another case reported the first human transvesical peritoneoscopy using a flexible ureteroscope during a standard laparoscopic robot-assisted prostatectomy[53].

The first natural orifice transluminal cholecystectomy in humans was performed in Strasbourg, France[54]. A 30-year-old woman with symptomatic cholelithiasis was submitted to cholecystectomy using a standard double-channel flexible gastroscope and standard endoscopic instruments. A 2-mm transabdominal needle port was used to insufflate carbon dioxide, to monitor the pneumoperitoneum, and to retract the gallbladder. Colpotomy was closed using conventional instruments. The patient had no post-operative pain and no scars, and was discharged on the second post-operative day. Shortly after that, the same technique was used by a team in Brazil, and by another in Italy[55,56].

In 2007, a group of investigators from Ohio, United States used transgastric peritoneoscopy after standard laparoscopy to diagnose pancreatic masses[57]. In 9 out of 10 patients, transgastric abdominal exploration corroborated the decision to proceed to open exploration made during traditional laparoscopic exploration. The average time of diagnostic laparoscopy was 12.3 min, compared to the 24.8 min taken for the transgastric route. Closure of the gastrotomy was obviated through its integration into the primary operation, whether that involved a resection with curative intent or palliation. No cross-contamination of the peritoneum or infectious complications was noted.

Other procedures using exclusively natural orifice transluminal procedures in humans have been performed - transgastric and transduodenal pancreatic necrosectomy[58], transvaginal incisional hernia repair[59], transvaginal liver, diaphragm, ovaries, and peritoneum biopsies[60], and transvaginal appendectomy[61]. This last one is especially important, as two of the three cases presented had an umbilical port inserted in order to complete appendectomy. As seen before in cholecystectomy, the use of a transabdominal port is essential to make natural orifice approaches feasible or at least easier at this time. Hybrid NOTES procedures are seen as a safe way to accomplish pure NOTES in the future. For this aim, hybrid procedures are developing in humans and achieving new goals like transvaginal nephrectomy[62], transrectal rectosigmoidectomy[63], sleeve gastrectomy[64], transvaginal liver resection[65], transvaginal splenectomy[66], transgastric cholecystectomy[67], transanal rectal cancer resection[43], intragastric stapled cystogastrostomy of a pancreatic pseudocyst[68], and adjustable gastric banding[69].

In 2009, de Sousa *et al*[70] published the first series of pure NOTES transvaginal cholecystectomies. The authors performed four cholecystectomies using two endoscopes introduced simultaneously in the abdominal cavity through a transvaginal incision. Dissection was accomplished with conventional endoscopic instruments. Ligation of the cystic duct and artery was performed using endoscopic clips. Vaginal closure was achieved using the direct-vision suture technique. More recently, Bessler *et al*[71] described a different technique for pure NOTES cholecystectomy in a 35-year-old-woman. Instead of using two endoscopes, the authors used an extra-long 5-mm articulating retractor placed into the abdomen *via* a separate colpotomy made under direct vision using the flexible endoscope in a retroflexed position. This method overcame the retracting limitations that obliged the use of a transabdominal port.

Despite all the enthusiasm around NOTES, other clinical advantages besides the absence of skin incision remain to be fully proven. Although most studies claim that greater operative time would be compensated by shorter hospital stays, prospective control studies are lacking[72]. Hensel *et al*[73] reported a retrospective case-control study where hybrid transvaginal cholecystectomy group showed a lower need for analgesics, faster mobilization, more comfortable recovery and a shorter hospital stay than the conventional laparoscopy group.

Finally, patients' perspectives and expectations about NOTES are not yet fully understood. An interesting questionnaire-based study was derived to identify their preferences between different available surgical options upon a hypothetical scenario of an acute appendicitis[74]. Single port surgery (SPS) was the most popular method followed by conventional laparoscopy. Open surgery and NOTES were the least preferred. Choosing between SPS and NOTES only, 80.6% opted for SPS, 11.8% NOTES, and 5.6% declined surgery. The most popular route of access for NOTES was oral (37.7%). Another study asked women about their concerns and opinions regarding transvaginal surgery[75]. The majority of women (68%) indicated that they would want a transvaginal procedure in the future because of decreased risk of hernia and decreased operative pain (90% and 93%, respectively), while only 39% were concerned with the improved cosmesis of NOTES surgery. Of the women polled, nulliparous women and those under age 45 years were significantly more often concerned with how transvaginal surgery may affect healthy sexual life and fertility issues. Of the women who would not prefer transvaginal surgery, a significant number indicated concerns over infectious issues.

THE FUTURE OF NOTES

NOTES promises a new and innovative era of minimal access surgery based on traditional laparoscopic and endoscopic techniques. Researchers all over the world are investigating ways to improve NOTES procedures in order to make it easier and safer. With careful development of new equipment and techniques, NOTES may be a reasonable option to conventional laparoscopic procedures. It may even become the method of choice for selected surgical procedures in the future.

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S-editor Tian L **L-editor** Rutherford A **E-editor** Li JY

Annex 2. Natural orifice transesophageal endoscopic surgery

Moreira-Pinto J, Ferreira A, Rolanda C, Correia-Pinto J. Natural orifice transesophageal endoscopic surgery: state of the art. Minim Invasive Surg 2012; 2012:896952.

Hindawi Publishing Corporation
Minimally Invasive Surgery
Volume 2012, Article ID 896952, 7 pages
doi:10.1155/2012/896952

Review Article

Natural Orifice Transesophageal Endoscopic Surgery: State of the Art

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Received 9 December 2011; Accepted 9 February 2012

Academic Editor: Luigi Boni

The main goal of Natural Orifice Transluminal Endoscopic Surgery (NOTES) is performing surgery avoiding skin incisions. Theoretical advantages of NOTES include decreased postoperative pain, reduction/elimination of general anesthesia, improved cosmetic outcomes, elimination of skin incision-related complications such as wound infections and hernias, and increased overall patient satisfaction. Although various forms of port creation to accomplish thoracic NOTES procedures have been proposed, transesophageal NOTES has been shown to be the most reliable one. The evolution of endoscopic submucosal transesophageal access resulted in the development of per-oral endoscopic myotomy (POEM), which had a fast transition to clinical practice. The authors present a review of the current state of the art concerning transesophageal NOTES, looking at its potential for diagnostic and therapeutic interventions as well as the hurdles yet to be overcome.

1. Introduction

Natural Orifice Transluminal Endoscopic Surgery (NOTES) is the name given to novel endoscopic interventions on internal organs performed through natural orifices. In this new approach, endoscopes enter the abdominal and thoracic cavities via any single or combination of natural orifices—mouth, urethra, vagina, and anus [1]. In fact, NOTES dates back to 1940s, when Decker performed the first culdoscopy using an endoscope passed through the rectouterine pouch to view pelvic organs and perform sterilization procedures [2]. These procedures were superseded by noninvasive ultrasound imaging for diagnostic purposes and laparoscopy for surgical purposes. Later, NOTES was to be reborn when Rao and Reddy presented the video of the first transgastric appendectomy at the 2004 Annual Conference of the Society of Gastrointestinal Endoscopy of India [3]. In a severely burnt patient, whose skin they could not incise, they used a therapeutic flexible gastroscope to reach his stomach. Then, they performed an inside-out gastrostomy and pushed the gastroscope through the gastric wall into the abdominal cavity. They looked for the appendix and performed the first ever transgastric appendectomy.

The first description of transgastric peritoneoscopy in porcine model published in paper was by Kallo et al. in 2004 [4]. Soon, other natural orifices were presented as good access points for NOTES. Pai et al. published transcolonic peritoneoscopy followed by a series of transcolonic procedures [5]. The access from below gives a good, direct view of the upper abdominal cavity. Having this in mind, Lima et al. presented transvesical endoscopic peritoneoscopy [6]. To accomplish NOTES procedures in the thorax and the mediastinum, Sumiyama et al. proposed a transesophageal access [7]. Transvesical-transdiaphragmatic [8], transgastric-transdiaphragmatic [9], and transtracheal [10] access have been suggested too. Even though, the transesophageal has been preferred as a direct entry to the thorax and permited several procedures in porcine model (Table 1) [11–19].

Table 1: Transesophageal NOTES procedures in animal studies.

Mediastinoscopy	Cardiomyotomy
Thoracoscopy	Esophagomyotomy
Lymphadenectomy	Vagotomy
Pleural biopsy	Sympathectomy
Myocardial and left atrium injection	Esophagectomy and end-to-end anastomosis*
Pericardial fenestration	Pulmonary lobectomy*
Epicardial ablation	Left atrial appendage ligation*

* With single transthoracic trocar assistance.

The main goal of NOTES is to avoid skin incisions and its associated complications, such as wound infections and hernias. Theoretical advantages of NOTES include reduction in hospital stay, faster return to bowel function, decreased post-operative pain, reduction/elimination of general anesthesia, performance of procedures in an outpatient or even office setting, possibly cost reduction, improved cosmetic outcomes, and increased overall patient satisfaction [1].

2. Transesophageal Approach

When Sumyiama et al. presented transesophageal access to the thorax and mediastinum, they used submucosal endoscopy with mucosal flap (SEMF) [7]. The authors injected saline into the esophageal submucosal layer creating a bleb and high-pressure carbon dioxide was used to perform a submucosal dissection. A biliary retrieval balloon was then inserted into the submucosal layer and was distended to enlarge the mucosal hole and create a 10 cm long submucosa tunnel. Subsequently, they used an endoscopic mucosal resection (EMR) cap (Olympus, Tokyo, Japan) to create a defect in the muscularis propria and the mediastinum was entered. The key of the method is the overlying mucosa which serves as a sealant flap minimizing the risk of soiling a body cavity with lumenal contents and the ease by which the entry point into the submucosal working space can be closed [20].

Several modifications have been described to SEMF (Figure 1). Mucosa can be incised using either needle knife, a prototype flexible CO_2 laser fiber (OmniGuide Inc., Cambridge, MA, USA), or a Duette Multiband mucosectomy device (Cook Medical, Winston-Salem, NC, USA) [12]. Besides biliary retrieval balloons, the creation of the submucosal tunnel has been achieved with air and blunt dissection using snare tips, closed forceps, EMR caps [12–15]. Division of the muscular layer has been described using needle knife, although the aspiration method of the EMR cap may reduce the risk of injury to any adjacent mediastinal structure [13]. The SEMF procedure has also been applied in the stomach to safely perform NOTES in the abdominal cavity [21].

According to *von Renteln* et al. working with the endoscope through a dissection tunnel limits endoscope movements and degrees of freedom, and major procedures tend to stretch open the submucosal tunnel resulting in a major defect or laceration [22]. On the other hand, Moyer et al. tested durability of submucosal endoscopic tunnel in the stomach and concluded that it tolerates the mechanical forces of peroral transgastric procedures provided that the organ resected is small to moderate in size ($<8 \times 3$ cm) [23].

With or without submucosal tunneling, transesophageal approach to the thoracic cavity is highly risky because of possible mechanical abrasion and trauma of surrounding structures [13, 22]. For that, Fritscher-Ravens et al. proposed endosonographically EUS-assisted transesophageal access. In a comparative study of NOTES alone against EUS-assisted NOTES procedures, the authors found that the last was superior in gaining access, identifying structures, and therefore avoiding major complications [24].

A different alternative was presented by Rolanda et al. single transthoracic trocar assistance for transesophageal NOTES [18]. As most thoracic procedures imply some time of postoperative tube drainage, a 12 mm incision was made in the thoracic wall and a 10 mm trocar was inserted before esophagotomy was performed. Using a 10 mm thoracoscope with a 5 mm working channel (Karl Storz, Tuttlingen, Germany) inserted through the transthoracic trocar, transesophageal port was safety created with thoracoscopic visual control. Moreover, other well-known problems of NOTES, such as tissue manipulation, suturing, and anastomosis establishment, were overlapped, because triangulation and countertraction were achieved using flexible instruments inserted through the gastroscope and rigid instruments inserted through the thoracoscope. Therefore, transesophageal NOTES with the assistance of a single transthoracic trocar can be used for highly complex thoracic procedures.

Recently, our group has presented transesophageal pulmonary lobectomy with survival assessment in porcine model, using this single transthoracic port assistance [19]. Besides using flexible instruments inserted through the gastroscope, we introduced several rigid instruments through an oroesophageal overtube: endstaplers (EndoPath, Ethicon Endo-Surgery, Cincinnati, OH, USA), SILS-Stich (SILS stitch, Covidien, Mansfield, MA, USA), and knot-pusher. Coordinating the movement of a rigid instruments through the mouth with the image provided by the thoracoscope made ligation of the right upper bronchus and its vessels possible and reliable. The 12 mm thoracic incision was crucial for acute air and liquid drainage. All the four animals in the survival group subsisted for 15 days [19].

Transesophageal NOTES with the assistance of a single transthoracic trocar might be the key to incisionless cardiac procedures. Our group has performed left atrial appendage (LAA) ligation in 4 acute and 6 survival porcine models (unpublished results). The instruments entering both through the gastroscope and the thoracoscope made triangulation very similar to the one experienced on exclusive thoracoscopic approach. The flexible endoscope had a good access to all aspects of the heart—using direct position to reach the base of the heart and retroflexion for its apex. Moreover, flexible gastroscope was useful to show some parts of the thoracic cavity that could not be visualized with the 0° optic of the operative thoracoscope, namely, lateral thoracic wall and the entire diaphragm. With exception of the one acute

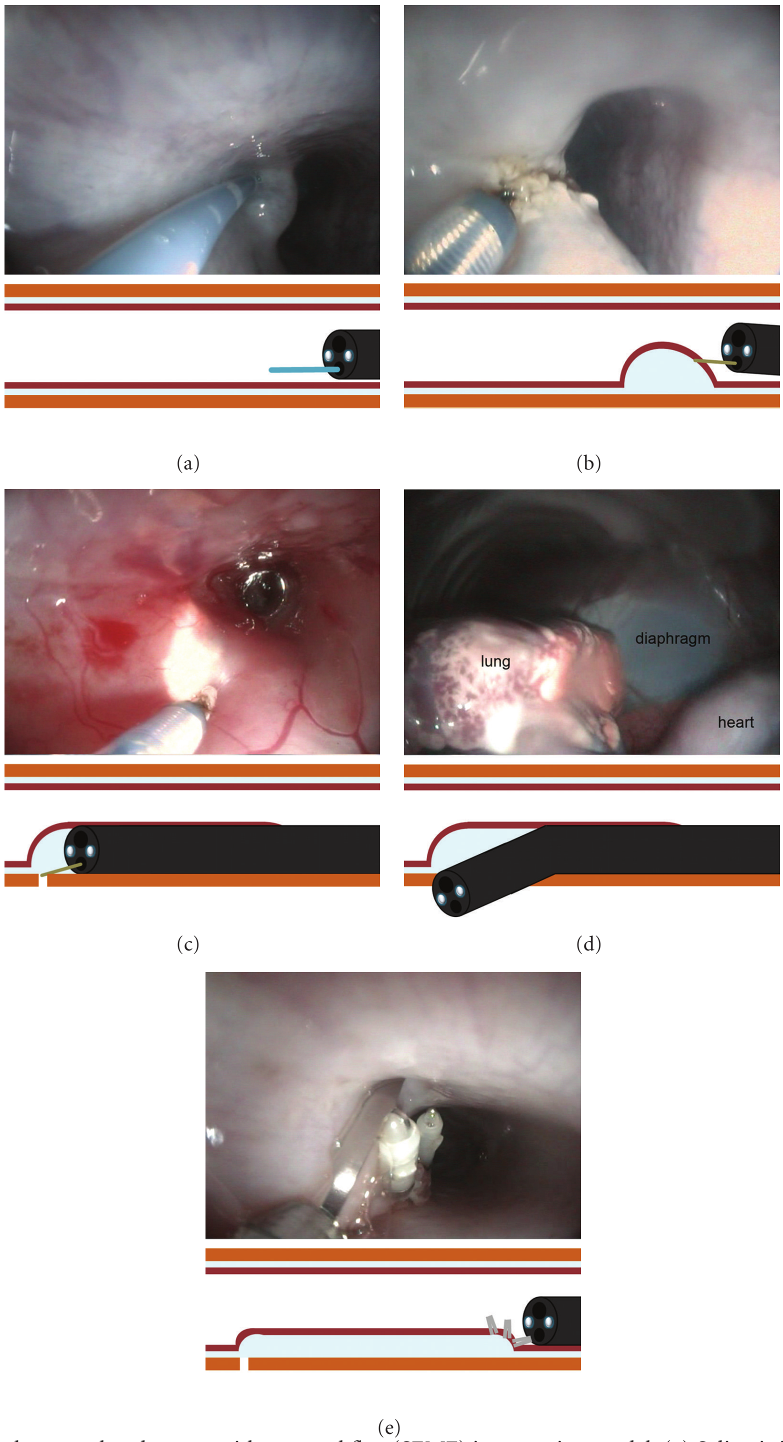

Figure 1: Transesophageal submucosal endoscopy with mucosal flap (SEMF) in a porcine model. (a) Saline is injected into the submucosal layer of the esophagus. (b) The mucosa of the bleb is incised using a needle knife. (c) A 10 cm tunnel is created using air and blunt dissection. The muscularis propria is incised at the distal end of the esophageal submucosal tunnel. (d) The endoscope is passed through the esophagotomy and the thoracic cavity is inspected. (e) Esophagotomy closure is achieved by mucosal flap adhesion. The mucosal defect is sutured using endoclips.

experiment which was terminated because of LAA rupture, all the other animals were kept alive until the end of the experiment. No adverse event occurred during the survival period. Complete LAA ligation was verified on necropsy, as LAA was fibrotic with the nylon endo-loop in place.

The NOTES revolution permitted evolution of the different natural orifices approaches themselves. The performance of endoscopic submucosal transesophageal myotomy is a perfect example of this. Pasricha et al. used SEMF to perform peroral endoscopic myotomy (POEM) in an experimental setting [25]. Soon after this, Inoue et al. reported the first clinical experience of POEM for the treatment of achalasia [26]. In 17 consecutive patients, there were no intraoperative or postoperative complications, and the occasions of inadvertent entry into the cardiac mucosa (2 patients) and the exposure of mediastinal tissue (4 patients) were without incident. Although POEM might not be considered a true NOTES procedure because it does not divide all the layers of the esophagus, it does use readily available endoscopic equipment and techniques and directly competes with a laparoscopic procedure [27].

3. Esophagotomy Closure

When SEMF is used to create transesophageal access, esophagotomy closure is easy, as the overlying mucosa serves as a sealant flap. Most authors use endoclips to close the defect of the mucosa, but in the early studies the mucosa was left open with good clinical outcomes [7, 12–14]. Turner et al. published a study comparing esophageal submucosal tunnel closure with a stent versus no closure [28]. In this study, the unstented group achieved endoscopic and histologic evidence of complete reepithelialization and healing (100%) at the mucosectomy site compared with the stented group (20%, $P = .048$). So, it seems that the placement of a covered esophageal stent prejudices healing of the mucosectomy site.

When direct incision esophagotomy is performed, a full-thickness healing of the mucosal and muscular layer must be achieved. Fritscher-Raves et al. compared endoscopic clip-closure (ECC) versus endoscopic suturing (ECS) versus thoracoscopic (TC) repair of a 2–2.5 cm esophageal incision [29]. ECS was achieved using a prototype suturing system that deploys a metal anchor with a nonabsorbable polypropylene thread (T-bar) on each side of the esophageal defect (CR Bard, Murray Hill, NJ; Ethicon Endosurgery, Cincinnati, OH, USA). The two threads were joined together using a small cylindrical suture-locking device, approximating both sides of the incision. Three to 5 pairs of T-bars were used to close the defect. Thoracoscopic repair took the longest time because of trocar placement and dissection of the periesophageal tissue for localization of the defect in the esophagus. Although ECC was the fastest technique, it could not achieve full-thickness repair of the esophageal wall. Moreover, larger gaping defects could not be bridged by the jaws of the clips. In contrast, ECS anchors were deployed across the entire esophageal wall and showed well-healed scares with the smallest remaining gaps. One of the disadvantages of T-bars is that placing them beyond the gastrointestinal wall cannot be performed under direct vision. So, the needle tip may harm or inadvertedly place a T-bar into an unwanted structure as reported in a previous study [30].

The novel over-the-scope clip (OTSC) system showed promising results for gastrostomy closure [31] and has been used in for closure of postoperative leaks following gastrectomy and primary repair after spontaneous acute esophageal perforation [32]. Cardiac septal occluders might be a valuable alternative. Repici et al. have recently reported the first human case of esophagus-tracheal fistula closure by using a cardiac septal occluder with good results [33]. Other prototype suturing/apposition devices might be of future use in esophagotomy closure, namely, Padlock-G clips (Aponos Medical, Kingston, NH, USA) [34], NDO Plicator (NDO Surgical Inc., Mansfield, MA, USA) [35], g-Cath/g-Prox (Usgi Medical Inc, San Clemente, CA, USA) [36], flexible Endostich (Covidien, North Haven, Conneticut, USA) [37], OverStich (Apollo Endosurgery, Austin, TX, USA) [38], Direct Drive Endoscopic System (DDES Boston Scientific, Natick, MA, USA) [39], Anubis-scope (Karl Storz, Tuttlingen, Germany) [40],and Endo-Samurai (Olympus, Tokyo, Japan) [41].

Von Reitein et al. presented a prototype self-expanding metal stent (SX-ELLA stent, ELLA-CS, Hradec Kralove, Czech Republic) for direct incision esophagotomy closure without any suture [22]. Fifteen-millimeter direct incision esophagotomies were created in 12 domestic pigs using a prototype endoscopic Maryland dissector (Ethicon Endosurgery, Cincinnati, OH, USA). Six animals were randomly assigned to open surgical repair and six animals to endoscopic closure using the self-expanding, covered, nitinol stent in a nonsurvival setting. Pressurized leak test results were not different for stent compared to surgical closures. Six animals underwent transesophageal endoscopic mediastinal interventions and survived for 17 days. Stents were extracted at day 10. All survival animals were found to have complete closure and adequate healing of the esophagotomies, without leakage or infectious complications.

Finally, the hybrid approach presented by Rolanda et al. might be useful for safe esophagotomy closure. Using a thoracoscope with a 5 mm working channel, the authors inserted a needle-holder and performed an end-to-end esophageal anastomosis with gastroscopic intruments assistance [18].

4. Mediastinum and Pneumothorax Management

Injecting air or carbon dioxide (CO_2) is a key component for adequate exposure and visualization, especially in thoracic NOTES. Air insufflated in an uncontrolled manner through the endoscope results in wide fluctuations in intrathoracic and intraperitoneal pressures, overdistension of the gastrointestinal tract, and adverse hemodynamic effects. Von Delius et al. studied the potentional cardiopulmonary effects of transesophageal mediastinoscopy in a porcine model, using a conventional gastroscope [42]. Air insufflation was manually performed and the pressure was monitored through the working port of the gastroscope. In 3 of the 8 pigs, there was pleural injury with tension pneumothorax, resulting in hemodynamic instability. In the remaining 5 pigs, median mediastinal pressure maintained was 4.5 mm Hg (mean 5.4 ± 2.2 mm Hg). In this uncomplicated mediastinoscopies, peak inspiratory pressures, pH, partial pressure of CO_2, and partial pressure of O_2 were not influenced.

Inadvertent high-pressure pneumomediastinum and pneumothorax have been major complications since the begining of thoracic NOTES [7, 12, 16]. Most authors use thoracic tube drainage for pressure relief. As CO_2 pressure control is also a main concern in abdominal endoscopic surgery, new insufflators have been adapted to both deliver and monitor CO_2 through the endoscope [43]. These may be of some use in transesophageal NOTES. Meanwhile, using a Veress needle or a transthoracic trocar may be a secure way to achieve good pneumothorax pressure control [18].

There is a great debate whether CO_2 or room air should be used for transesophageal NOTES. CO_2 is far more soluble in blood than air and fatal CO_2 embolism is rare. The effect of CO_2 with respect to laparoscopy has suggested an overall attenuated inflammatory response that may provide a further immunologic benefit. Conversely, room air laparoscopy has been shown to generate a greater inflammatory response, but a recent case-control study did not find a significant difference between the peritoneal inflammatory response of NOTES versus laparoscopy with CO_2 and air pneumoperitoneum [44].

Even for intraesophageal endoscopic surgery, the question if either air or CO_2-insufflation should be used is relevant. A study by Uemura et al. found a decreased need for midazolam in patients undergoing esophageal endoscopic submucosal dissection with CO_2-insufflation when compared to air-insufflation. The authors attributed this decreased need for midazolam to decreased procedural pain [45]. In human POEM procedures, only CO_2-insufflation has been used [26, 46]. Inoue et al. reported that none of the 17 patients in their series had postoperative subcutaneous emphysema, but CT scan just after procedure revealed a small amount of CO_2 deposition in the paraesophageal mediastinum. The authors suggest that positive pressure ventilation with intratracheal intubation should be maintained at higher pressures than those generated by endoscopic CO_2-insufflation in order not only to reduce mediastinal emphysema but also to reduce the risk of air embolization [26].

In their series of 5 patients undergoing POEM, Swaanström et al. observed the development of pneumoperitoneum in 3 patients and placement of a Veress needle was necessary to decompress it [46]. According to the authors, Inoue described this occurrence as well in 10% of this most recent series of more than 100 patients (personal communication) and theorized that it might occur due to gas permeation through the remarkably thin longitudinal muscle fibers of the esophagus [46].

5. Infection Prevention

Since the beginning of NOTES procedures, sterility has been a hurdle. Infection must be prevented by using a clean access site. Most transesophageal protocols follow a 12–24-hour liquid formula diet, intravenous antibiotics and esophageal and stomach irrigation with saline or iodopovidone solution. Despite these precautions, even a sterile overtube used to protect the endoscope from oral contamination becomes contaminated on oral insertion and can transport bacteria to the esophagus, the mediastinum, and the thorax.

Several infectious complications have been reported. In a study by Fritscher et al. two out of 12 pigs had reflux of gastric contents into the esophagus that resulted in spillage through the esophagotomy [28]. The study protocol included 12-hour fasting period before surgery and a 3-day antibiotherapy with enrofloxacin. Despite this, one animal died of severe mediastinitis, whereas the other one developed a subclinical mediastinal abscess found on necropsy. The authors suggested that careful aspiration of gastric contents at the beginning of the procedure should always be performed. Also, the authors concluded that 12 hours of fasting may be too short time to clear the stomach of the animals well enough. In a previous study by Gee et al., one out of four animals developed submucosal abscess, despite 24 h liquid diet, esophagus and stomach lavage with iodopovidone solution and cefazolin injection preoperatively [14].

There is also some controversy about the need for endoscope sterilization. In a recent literature review, Spaun et al. concluded that, although difficult, it is possible to terminally sterilize flexible endoscopes. Steris System 1TM that uses 0.2% peracetic acid was the cheapest and fastest sterilization method and scored second in the risk of recontamination. Ethylene oxide gas (ETO) sterilization has the lowest risk of recontamination but is the slowest and most expensive method. The authors recommend sterile instrumentation for clinical NOTES until well-designed and randomized clinical trials are available and guidelines are published [47].

When transferring the results from animal experiments to human settings, one should keep in mind that anatomy and physiology of the esophagus and the mediastinum in humans are somewhat different from those of the pig, especially with regard to wall structure, motility, and infection pathophysiology of the mediastinum. In humans, a perforation of the esophagus causes severe complications or even death in at least 30–50% of cases [48]. In human POEM, patients are placed on a clear liquid diet 24 hours and given a single preoperative dose of a first generation cephalosporin [46]. Although published series account for a short number of patients, no infectious complications were reported. Neither studies specify if the flexible endoscope was either completely sterilized or conventionally disinfected.

6. Conclusions

Transesophageal NOTES offers new possibilities in less invasive access to mediastinal and thoracic cavities. Ongoing NOTES revolution permitted the development of esophageal submucosal endoscopic techniques with almost immediate human application. POEM is a perfect example of this. Theoretical advantages of transesophageal NOTES warrant the continuation of research, although some hurdles are to be overcome. The critical nature of the organs that involve the esophagus, the risk of hemodynamic instability related to pressure pneumomediastinum and pneumothorax, and potential infectious complications call for caution when transition to human practice.

A hybrid NOTES approach, adding transthoracic assistance, might be the key to safe human translation, as it gives visual control of transesophageal port creation (Figure 2), it may improve esophagotomy closure, it permits triangulation and countertraction using flexible instruments inserted

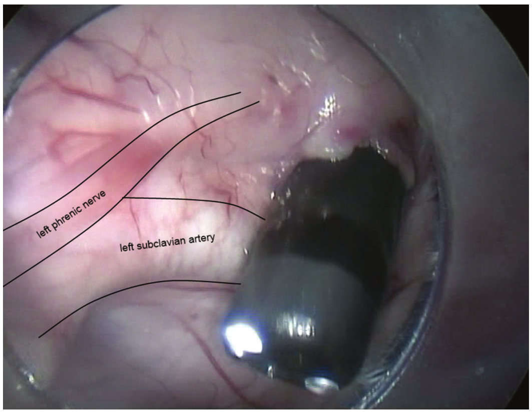

Figure 2: Transthoracic visual control of transesophageal port creation in the upper third of the esophagus (porcine model).

through the gastroscope and rigid instruments inserted through the thoracoscope, and it gives a good intrathoracic pressure control and pneumothorax drainage.

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Annex 3. Hybrid thoracic NOTES esophageal atresia repair

Henriques-Coelho T, Soares TR, Miranda A, Moreira-Pinto J, Correia-Pinto J. transthoracic single port with per-oral assistance: an animal experiment to assess a less invasive technique for human esophageal atresia repair. J Laparoendosc Adv Surg Tech A. 2012; 22: 1021-1027.

JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES
Volume 22, Number 10, 2012

DOI: 10.1089/lap.2012.0136

Transthoracic Single Port with Peroral Assistance: An Animal Experiment to Assess a Less Invasive Technique for Human Esophageal Atresia Repair

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João Moreira-Pinto, MD,[1,2,5] and Jorge Correia-Pinto, MD, PhD[1,2,5]

Abstract

Thoracoscopic repair of esophageal atresia has becoming the gold standard in many centers because it allows a better cosmetic result and avoids the musculoskeletal sequelae of a thoracotomy. Natural orifice translumenal endocopic surgery (NOTES) is a new surgical paradigm, and its human application has already been started in some procedures. In the present study, we explore the feasibility of performing an esophagoesophageal anastomosis using a single transthoracic single port combined with a peroral access in a rabbit model to simulate repair of esophageal atresia by hybrid NOTES in a human newborn. Adult male rabbits (*Oryctolagus cuniculus*, $n=28$) were used to perform the surgical protocol. We used a transthoracic telescope with a 3-mm working channel and a flexible endoscope with a 2.2-mm working channel by peroral access. We performed total esophagotomy with peroral scissors followed by an esophagoesophageal anastomosis achieved with a rigid transthoracic scope helped by the peroral operator. Extracorporeal transthoracic knots were performed to complete the anastomosis. The anastomoses were examined *in loco* and *ex loco*, after animal sacrifice. We successfully accomplished a complete esophageal anastomosis in all rabbits using a combination of transthoracic and peroral 3-mm instruments. This study provides important insights for a possible translation of hybrid NOTES to human newborns with esophageal atresia. Forward studies to accomplish their feasibility in human newborns will still be necessary.

Introduction

The first successful one-stage surgical correction of esophageal atresia (EA)[1] was described by Haight and Towsley, in 1943. After this report, many other studies succeeded, and posterolateral right extrapleural thoracotomy became the gold standard correction of EA.[1] In 1999, with advances of technology, knowledge, and surgical skills, the first thoracoscopic repair of EA without tracheoesophageal fistula (TEF) was performed at the International Pediatric Surgical Endoscopy meeting, in Berlin.[2] One year later, Rothenberg[3] performed the first thoracoscopic correction of EA with TEF. Since then, many other authors have adopted the surgical correction of EA by the thoracoscopic approach, and it is already the gold standard in many centers.[4,5] After laparoscopy and thoracoscopy, a new paradigm shift was beginning to emerge: natural orifice translumenal endoscopic surgery (NOTES). Several complex surgeries like cholecystectomy[6] or nephrectomy[7] have been described by our group in experimental porcine models. Roughly 10 years later, NOTES could be the next evolution step to correct this anomaly.

The transition of NOTES to humans has been limited by the inability to safely close the viscera wall.[8] Increasing numbers of reports are describing the use of hybrid NOTES or laparoscopy assisted by NOTES in humans.[9] Regarding pediatric surgery, the peroral route to thoracic procedures seems to be a very attractive approach. Our group previously showed in an

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Videos of this technique can be found online at www.liebertpub.com/lap adult porcine model that an esophagoesophageal anastomosis could be performed by hybrid NOTES using a peroral and thoracoscopic approach.[10] However, this study was designed to simulate a surgery in human adults and not to explore the feasibility of performing an esophagoesophageal anastomosis in a newborn with EA. In the present work, we tested the possibility of performing hybrid thoracoscopic and peroral NOTES in a rabbit model to simulate the human newborn.

Materials and Methods

Study design

This project was approved by the ethical review boards of Minho University (Braga, Portugal). We used 28 adult male rabbits (*Oryctolagus cuniculus*) as an experimental model for the human newborn. Twenty animals were used for the learning curve, and in eight animals the experimental protocol was achieved completely. The surgical procedure involved esophageal dissection, esophageal section, and esophagoesophageal anastomosis using a single transthoracic trocar assisted by a peroral access. The surgical instruments used in this protocol included a 10-mm trocar (Thoracoport®; Covidien), a 22 French (7.3-mm) rigid telescope with a 3-mm working channel (model 27092 AMA; Karl Storz), a 16 French (5.3-mm) flexible telescope with a 6.5-French (2.2-mm) working channel (model 11272 VP; Karl Storz), a 5-mm modified endotracheal tube with a valve system (model 112482; Rusch; Teleflex), 3-mm instruments (Karl Storz) consisting of a knot-pusher, scissors, needle holders, dissector, and grasping forceps, a 6 French (2-mm) nasogastric tube (model 12027183; Unomedical), and 5-0 polydioxanone wire (Ethicon).

Presurgical procedures

Adult male rabbits, weighting between 2 and 3 kg, were given a liquid diet 12 hours before the procedure. All procedures were performed using general anesthesia. Preanesthesia medication consisted of buprenorphine (0.03 mg/kg, s.c.) (Budale; Dechra) followed 1 hour later by ketamine (25 mg/kg, s.c.) (Imalgene 1000; Merial Portuguesa—Saúde Animal), and medetomidine hydrochloride (0.5 mg/kg, s.c.) (DorbeneVet, EsteveDomitor; Pfizer Saúde Animal). A venous access was obtained through an intravenous line placed in the marginal ear vein, and anesthesia was maintained with ketamine (10 mg/kg/hour, i.v.). All animals were sacrificed with a barbiturate overdose (sodium pentobarbital, 100 mg/kg, i.v.) (Eutasil; CevaSaúdeAnimal).

Ergonomics

The layout of the room is represented in Figure 1. The animal was positioned at one end of the surgical table in the prone position. The thoracoscopic operator stood at one side of the operating table. The anesthetist and the peroral operator were positioned each one at one end side of the table. Monitors were positioned in front of each operator.

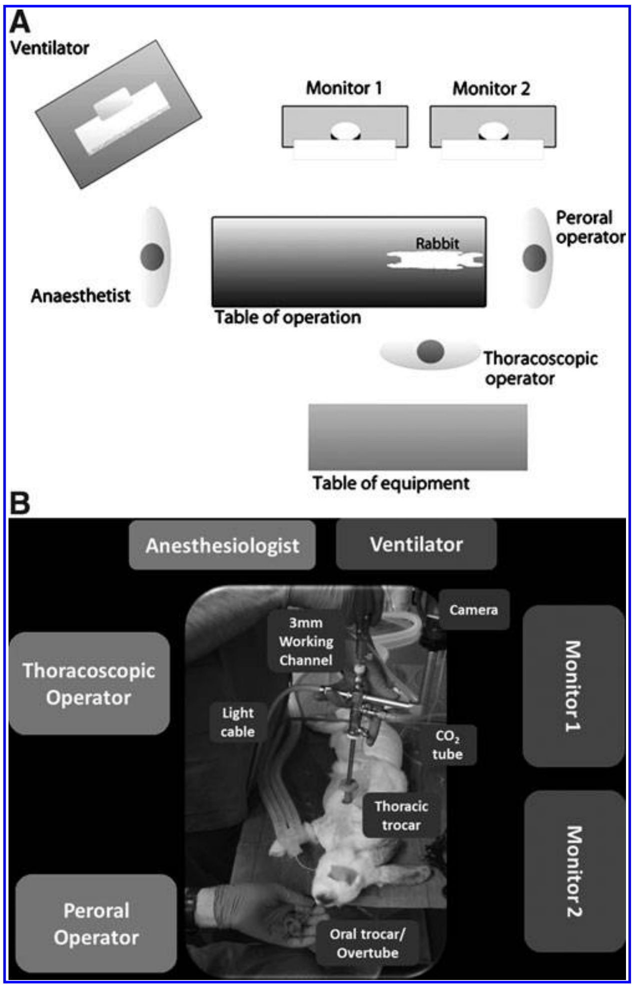

FIG. 1. (**A** and **B**) Layout of the operating room. Monitor 1 was for the peroral operator; Monitor 2 was for the thoracoscopic operator.

Surgical procedure

After the animal was put under general anesthesia, a tracheostomy was performed, and mechanical ventilation was started. The rabbits were placed in the prone position. A 10-mm transthoracic trocar was positioned immediately below to the lower end of the right scapula. The rigid telescope

FIG. 2. Major steps executed during the protocol. Dissection was performed by the transthoracic operator, whereas the peroral operator accessed the esophageal lumen with a flexible endoscope, permitting him to take lateral movements and **(A)** up and **(B)** down movements. Complete esophagotomy was achieved by a peroral scissor **(C)** helped by a transthoracic grasper, which held the distal esophageal portion in the end of the section **(D)**. After the peroral operator grasped the distal section of the esophagus **(E)**, the transthoracic operator started the anastomosis with the first stitch **(F)** and ended the extracorporeal knot with a knot-pusher **(G)**. **(H)** The excess wire was cut by a transthoracic scissors. A nasogastric tube was introduced through the mouth to achieve the sectioned esophagus. A transthoracic forceps hold the nasogastric tube **(I)** and manipulated it to the intraluminal space of the distal esophageal portion **(J)**. The anastomosis process was continued **(K)** until it was completed **(L)**.

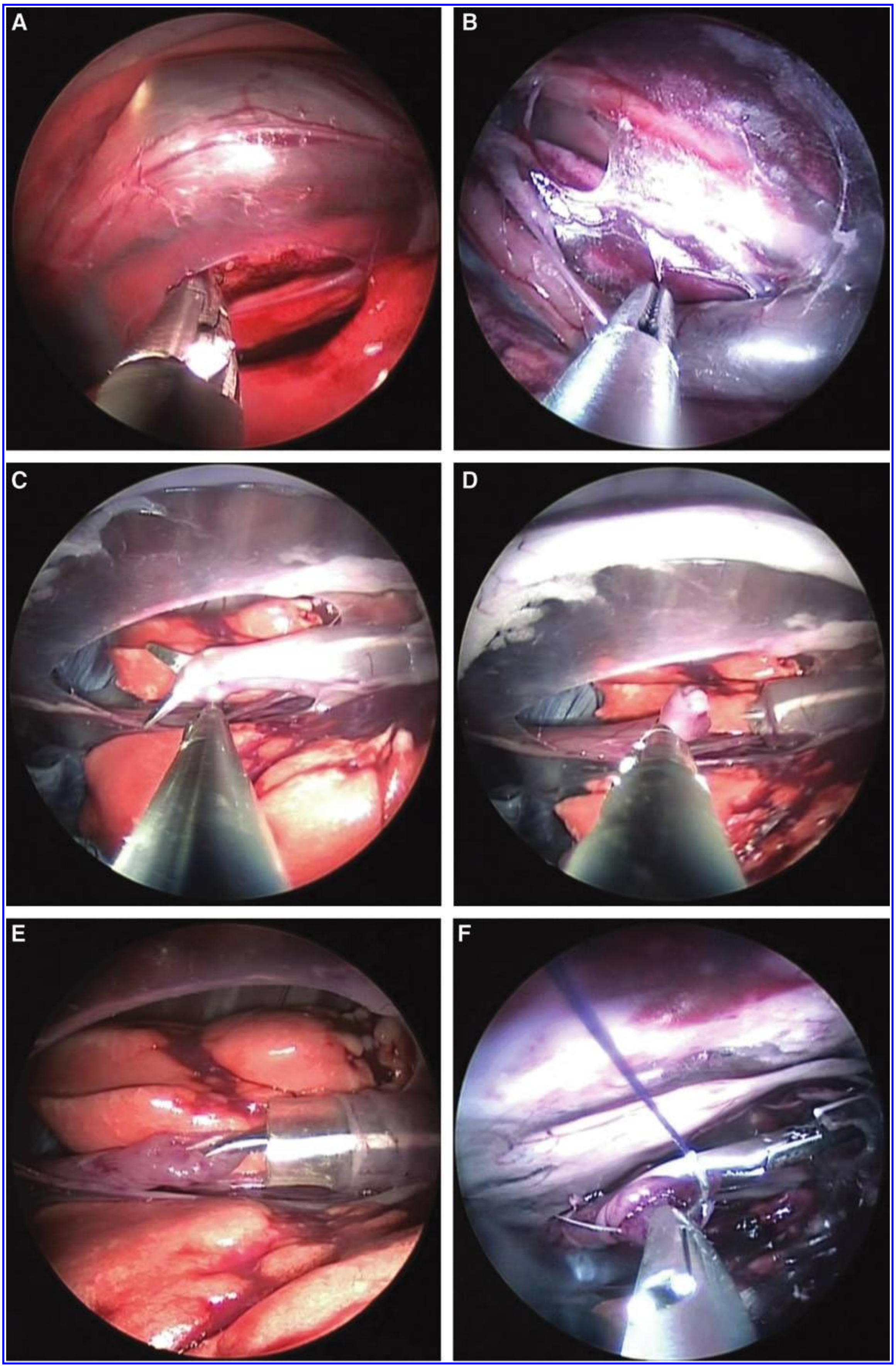

FIG. 2. (*continued*)

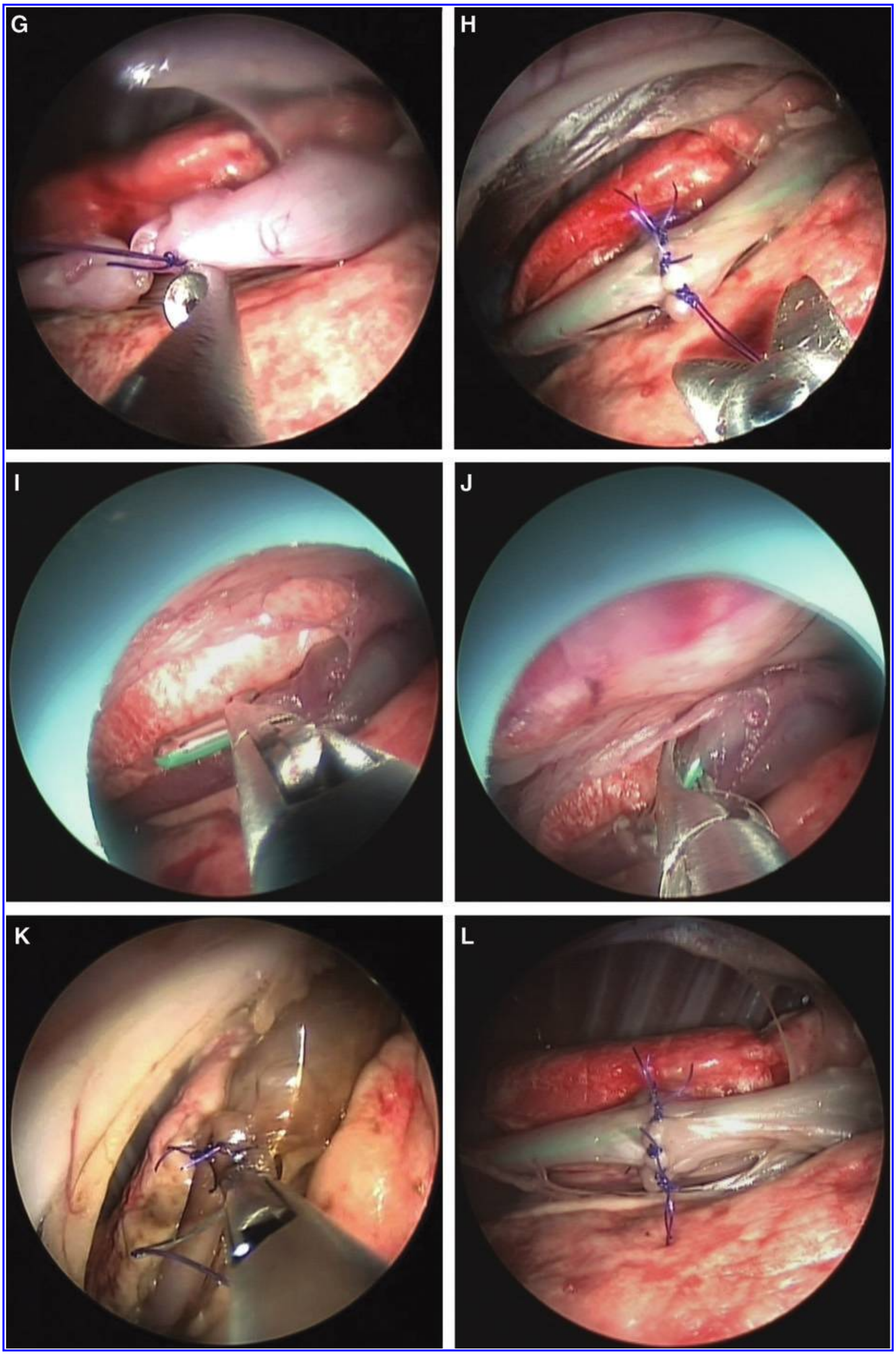

FIG. 2. (Continued).

(thoracoscope) with 3-mm working channel and a CO_2 insufflator (maximum pressure of 6 mm Hg) were used. The flexible telescope (endoscope) with a 6.5 French (2.2-mm) working channel was introduced through the mouth and moved to the esophagus. Esophageal dissection was carried out via the transthoracic approach using a 3-mm dissector forceps helped by the lateral and up-and-down movements performed by the peroral endoscope. A wire guide was introduced through the working channel of the peroral endoscope to the stomach, and the endoscope was removed. A modified 5-mm endotracheal tube with a valve system at the distal end was introduced until the proximal third of the esophagus and worked as an overtube or a flexible trocar. The esophagus was grasped near the distal end of the endotracheal tube using a 3-mm transthoracic dissector, and the esophagus was sectioned using the 3-mm peroral scissors. The distal portion of the sectioned esophagus was held by a 3-mm peroral dissector. The esophagoesophageal anastomosis was performed with 5-0 polydioxanone suture using a 3-mm transthoracic needle holder. The first esophagoesophageal stitch was passed in the posterior wall using a transthoracic needle holder helped by a peroral dissector in order to include all layers of the esophageal wall. All the knots were performed extracorporeally using a transthoracic knot-pusher. After two or three stitches on the posterior wall, a nasogastric tube was inserted through the mouth. In total, 7–10 single sutures were made. The rabbits were sacrificed after surgery. A segmental esophagectomy was performed to collect an esophageal section with the anastomosis, and its integrity was checked in its external and internal surface.

Results

Learning curve

During the learning curve we experienced several technical difficulties. We tested different trocars, instruments, and techniques of dissection, section, and anastomosis until we achieved the final surgical protocol presented above. One of the difficulties was related to the decrease of intrathoracic CO_2 pressure after esophageal section and introduction of the modified endotracheal tube because a communication was opened between the mediastinum and the exterior through the esophagus. The problem was solved with the insertion of a valve system in the proximal end of the endotracheal tube. A technique to complete intracorporeal knots was developed, but it was abandoned because of its complexity and difficulty. We adopted the use of extracorporeal knots, which were simpler, faster, and more effective to accomplish esophageal anastomosis. Another difficulty was the intercostal hemorrhage caused during the manipulation of the suture needle that in most of the cases prevented the progression of the surgical procedure. This problem was solved after the team gained experience with the technique.

Surgical procedure

The surgical procedure is summarized step-by-step in Figure 2 and Supplementary Video (Supplementary Data are available online at www.liebertpub.com/lap). The lower end of the right scapula revealed an ideal access point to introduce the trocar. The location of the transthoracic port associated with the animal in the prone position and CO_2 insufflation permitted us to obtain a good visualization of the esophagus without the need of other instruments or techniques. For the first three stitches, the peroral dissector was helpful in two aspects: (1) to put the distal esophageal end close to the proximal esophageal end and (2) to include all the layers of the esophageal wall in the sutures. The first stitch, in particular, was the most difficult to perform because of the lack of stability of the esophagus (Fig. 2F). A nasogastric tube was inserted after the first two to three stitches, turning the anastomosis easier and faster to perform (Fig. 2I and J). However, the insertion of the nasogastric tube was again a challenging step, requiring an optimal coordination between the thoracoscopic and peroral operators. The anastomosis procedure was completed dominantly by the transthoracic needle holder helped by peroral rotation of the esophagus. Extracorporeal knots were performed with a 3-mm knot-pusher inserted through the thoracoscope (Fig. 2G). This technique permitted us to obtain an optimal view of the knotting process, easily controlling the pressure applied to each knot, and to decrease operative time. The remaining wire was cut transthoracically without any difficulty. Pearls and pitfalls of the protocol identified by the group are summarized in Table 1. The mean time to perform the surgical procedure in the eight rabbits—including dissection, esophagotomy, and anastomosis—was 85 minutes (range, 62–137 minutes). At the end of the procedure, the final aspect of the anastomosis was properly checked (Fig. 2L). Additional stitches were performed as much as necessary. The manipulation of the instruments needs to be cautious because of the proximity with the intercostal vascular structures. After sacrificing the animals, we performed a segmental esophagectomy to study the anastomosis closely. We verified a complete anastomosis in all cases, with the incorporation of the mucosa in all stitches (Fig. 3).

Table 1. Pearls and Pitfalls of the Protocol Identified by This Study

Pearls	Transthoracic trocar at the lower end of the right scapula
	Coordination between operators
	Peroral use of conventional 3-mm instruments
	Esophageal dissection helped by peroral endoscope
Pitfalls	First stitch
	Introduction of the nasogastric tube
	Intercostal vessels' proximity to surgical maneuvers

Discussion

Thoracoscopic repair of EA includes obvious advantages like better visualization of the surgical field, less postoperative pain, better cosmesis, and fewer musculoskeletal sequelae.[4] Some studies, including one multicenter analysis, suggested that thoracoscopic correction of EA with TEF can be safely performed by experienced surgeons and had comparable outcomes with thoracotomy.[4] Currently, this surgical technique is becoming the gold standard for EA correction in several centers.[4,5] However, a new era is emerging, and three or four transthoracic ports might be too much for a 21st century minimally invasive procedure. Although the first NOTES approach was a transvaginal procedure described by Decker and Cherry[11] in 1944, the enthusiasm about this technique

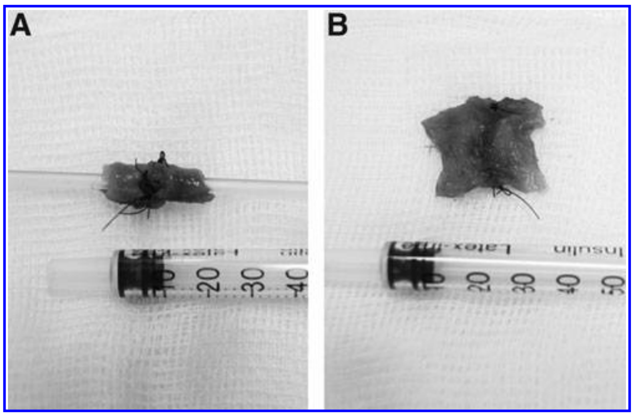

FIG. 3. **(A)** External and **(B)** internal views of the esophageal anastomosis.

only started six decades later. Starting in 2004 with a human transgastric appendectomy performed by Reddy and Rao,[12] NOTES brought a new set of opportunities. All possible approaches were explored: transgastric,[13] transvesical,[14] transcolonic,[15] and transesophageal[16] accesses. The potential advantages of NOTES over laparoscopy and thoracoscopy might include (1) reduction of general anesthesia use, (2) decrease in hospitalization time and postoperative pain, (3) prevention of skin incision complications (wound infection and hernias), (4) increment of outpatient regimen, (5) faster return of bowel function, (6) better cosmetic outcomes, and (7) increase in overall patient satisfaction.[9] Besides all these advantages, pure NOTES still has some limitations in the present.

A pure peroral approach might have some disadvantages like the extreme difficulty of creating triangulation, the precarious view of the work field, and, concomitantly, the increased risk of leakage resulting from an incomplete esophageal closure. Hybrid NOTES represents the best of the two fields—thoracoscopy and NOTES—because it allows a reduction of the number of transthoracic ports and overrides some of the limitations of pure NOTES. Using a transthoracic access combined with a peroral route, triangulation and countertraction can be achieved. Moreover, the excellent thoracoscopic visualization of the work field is profitable, and the thoracic incision can be used to place a drainage tube postoperatively.

EA can be an excellent congenital malformation candidate for peroral hybrid NOTES. At present, the upper esophageal pouch is only used for the introduction of the nasogastric tube, but in our opinion the upper esophageal pouch could potentially be a route for the thoracic cavity. Rolanda et al.[10] described a peroral esophageal segmentectomy and an anastomosis with a single 12-mm transthoracic trocar in an adult porcine model. The authors demonstrated the reliability of performing this technique in a large animal model. In the present study, we demonstrated the feasibility of combining the peroral and transthoracic routes to perform an esophagoesophageal anastomosis in rabbits. This animal model perfectly simulates the human newborn and is a well-established model to train pediatric surgeons in neonatal minimally invasive procedures.[17] The anatomic constitution of the rabbit simulates the newborn size, allowing the use of 3-mm instruments in a very limited space, as happens in human newborns. In this work, we explored the prone position of the animal to amplify our field of work. The prone position is being explored in patients in order to easily manipulate the esophagus.[18] This approach was previously explored in our department by Rolanda et al.,[10] stating the advantage to easily access the mediastinum with the help of the gravity, to use lower CO_2 pressures, and to decrease the time of the procedure. In thoracoscopic repair of EA, different centers are using the partially prone position of the patient at 30–45°,[4,19] and a fourth port is sometimes applied to retract the lungs.[4,19] A completely prone position may be more helpful than a partial one.

The great innovation of this study is the possibility of performing an EA correction with just one transthoracic port, in contrast to the classic thoracoscopy, which uses three or four trocars.[4,19] The use of a 10-mm trocar might be considered more invasive than three 5-mm trocars but still is a single incision. This trocar size was used to introduce the camera with the working channel. We might anticipate that the miniaturization of this kind of telescope will allow the use of smaller trocars in the future. The peroral flexible endoscope allowed us to achieve the esophageal lumen without difficulties and to easily mobilize it. The three-dimensional movements of the flexible endoscope allowed us to surpass the inconvenience of using just one transthoracic trocar to perform esophageal dissection. In a human newborn with EA, we might anticipate that this peroral approach could facilitate transthoracic dissection of the upper esophageal pouch. Additionally, cutting the proximal pouch with peroral scissors could be of great help in human newborns. Again, the possibility of grasping the lower pouch using this access can be useful for the first esophageal stitch. In this study, the mean operative time was 85 minutes. The average surgical time for thoracoscopic repair of EA with TEF is 130 minutes, as was reported by a multi-institutional study.[4] In the present study we did not perform dissection and ligation of the distal TEF, but we could anticipate that using a peroral gasper combined by a transthoracic dissector, it would be possible to perform this step. We demonstrated the feasibility of an esophageal anastomosis using a single transthoracic trocar with a similar time interval as using three or four transthoracic trocars. This surgical technique, combining peroral and transthoracic approaches, demands a well-synchronized performance between the surgeon and the first assistant to guarantee optimal results. Whereas in thoracoscopy or laparoscopy the same surgeon performs all the movements with both hands, in hybrid NOTES it is necessary to have an operator in each port. A good coordination between them is essential, permitting them to obtain synchronized movements as if the hands of each operator belonged to the same surgeon. Our team has already proved in other procedures, namely, cholecystectomy[6] and nephrectomy,[7] that the coordination between two operators is demanding but can be achieved with training.

We identified some limitations in the present study: (1) tracheostomy to ventilate rabbits and (2) lack of a true EA with TEF, the most common type of EA. During our learning curve, we abandoned the endotracheal intubation and started to perform tracheostomy to ventilate the animal. An endotracheal tube would make hard to introduce other instrumentation through the peroral route. To overcome this problem in humans, we suggest a nasotracheal tube, instead of using an orotracheal tube. The present work was a non-survival study using normal rabbits without EA. This fact did not allow us to explore the feasibility and safety of performing some technical procedures like TEF ligation. It might be important to simulate a TEF in an animal model or, ideally, translate this study to a deceased newborn with EA and distal TEF. Nevertheless, we believe in the viability of this approach in a human newborn because ligation of TEF is performed by many groups with a simple clip,[4] a maneuver that could be easily performed using transthoracic and peroral routes. This approach would imply a change in the surgical human routine—the first step would be the dissection and opening of the upper esophageal pouch to establish the peroral trocar before performing distal esophageal dissection and TEF ligation.

In conclusion, this is a proof-of-principle study that demonstrates the feasibility of performing an esophageal anastomosis combining a single transthoracic port with a peroral port in a rabbit model that simulates the human newborn. This study provides several important insights into the translation of hybrid NOTES repair for human newborns with EA. We anticipate that in the near future, the peroral route will replace at least one, if not two, transthoracic trocars.

Acknowledgments

This project was funded by a 2010 IPEG research grant.

Disclosure Statement

J.C.-P. is a consultant/adviser for Karl Storz (Tuttlingen, Germany). T.H.-C., T.R.S., A.M., and J.M.-P. declare no competing financial interests exist.

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