TRANSTHORACIC SINGLE PORT WITH PERORAL ASSISTANCE: AN ANIMAL EXPERIMENT TO ASSESS A LESS INVASIVE TECHNIQUE FOR HUMAN ESOPHAGEAL ATRESIA REPAIR

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Abstract:
Thoracoscopic repair of esophageal atresia has becoming the gold standard in many centers since it allows a better cosmetic result and avoids the musculoskeletal sequelae of a thoracotomy. Natural Orifices Transluminal Endoscopic Surgery (NOTES) is a new surgical paradigm and its human application was already started in some procedures. In the present study, we explore the feasibility to perform an esophago-esophageal 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 utilized 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 esophago-esophageal anastomosis with rigid transthoracic scope helped by peroral operator. Extracorporeal...
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Running Title

Hybrid NOTES for esophageal atresia repair

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ABSTRACT

Thoracoscopic repair of esophageal atresia has becoming the gold standard in many centers since it allows a better cosmetic result and avoids the musculoskeletal sequelae of a thoracotomy. Natural Orifices Transluminal Endoscopic Surgery (NOTES) is a new surgical paradigm and its human application was already started in some procedures. In the present study, we explore the feasibility to perform an esophago-esophageal 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.

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We successfully accomplished a complete esophageal anastomosis in all rabbits using a combination of transthoracic and peroral 3mm 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) was described by Haight and Towsley, in 1943 [1]. After this report, many other studies succeeded and posterolateral right extrapleural thoracotomy became the gold standard correction of EA [1]. In 1999, with the advance of the technology, knowledge and surgical skills, the first thoracoscopic repair of EA without TEF was performed at the International Pediatric Surgical Endoscopy meeting, in Berlin [2]. One year later, Rothenberg performed the first thoracoscopic correction of EA with TEF [3]. Since then, many others authors adopted the surgical correction of EA by 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: the Natural Orifice Translumenal Endoscopic Surgery – popularly known as 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 incapability of safety closure of 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, peroral route to thoracic procedures seems to be a very attractive approach. Our group previously showed in an adult porcine model that an esophago-esophageal 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 to perform an esophago-esophageal anastomosis in a newborn with EA. In the present work, we tested the possibility to perform hybrid thoracoscopic and peroral NOTES in a rabbit model to simulate human newborn.
MATERIAL AND METHODS

Study design

This project was approved by ethical review boards of Minho University (Braga, Portugal) and supported with the IPEG 2010 Research Grant Award. We used 28 adult male rabbits (Oryctolagus cuniculus) as an experimental model for human newborn. Twenty of them were used for learning curve and in eight animals the experimental protocol was achieved completely. The surgical procedure involved esophageal dissection, esophageal section and esophago-esophageal 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, USA), a 22 Fr (7.3 mm) rigide telescope with a 3 mm working channel (27092 AMA, Karl Storz, Germany), a 16 Fr (5.3 mm) flexible telescope with a 6.5 Fr (2.2mm) working channel (11272 VP, Karl Storz, Germany), a 5 mm modified endotracheal tube with a valve system (112482, Rusch, Teleflex, Malaysia), 3 mm instruments (Karl Storz, Germany) - a knot-pusher, scissors, needle holders, dissector and grasping forceps – a 6 Fr (2mm) nasogastric tube (12027183, Unomedical) and 5-0 polydioxanone wire (PDS, Ethicon).

Pre-surgical procedures

Adult male rabbits, weighting between 2 and 3 kilograms, were submitted to a liquid diet 12 hours before the procedure. All procedures were performed using general anesthesia. Pre-anesthesia medication consisted of buprenorphine (0.03 mg/kg, subcutaneously (SC)) (Budale, Dechra, United Kingdom) followed one hour later by ketamine (25 mg/kg, SC) (Imalgene 1000, Merial Portuguesa—Saúde Animal, Portugal) and medetomidine hydrochloride (0.5 mg/kg, SC) (DorbeneVet, EsteveDomitor, Pfizer Saúde Animal, Portugal). A venous access was obtained through an intravenous line placed in the marginal ear vein and anesthesia was maintained with ketamine (10 mg/kg/h; IV). All animals were sacrificed with a barbiturate overdose - sodium pentobarbital (100 mg/kg, IV) (Eutasil, CevaSaúdeAnimal, Portugal).
Ergonomics

The layout of the room is represented in figure 1. The animal was positioned in one end of the surgical table in prone position. Thoracoscopic operator was stood at one side of the operation table. Anesthetist and peroral operator were positioned each one at one end side of the table. Monitors were positioned in front of each operator.

Surgical procedure

After general anesthesia, a tracheostomy was performed and the mechanical ventilation was started. The rabbits were placed in prone position. A 10 mm transthoracic trocar was positioned immediately below to the lower end of the right scapula. The rigid telescope (thoracoscope) with 3 mm working channel and a CO\textsubscript{2} insufflator (maximum pressure of 6 mmHg). The flexible telescope (endoscope) with a 6.5 Fr (2.2mm) working channel was introduced through the mouth and moved to the esophagus. Esophageal dissection was carried out via transthoracic approach using a 3 mm dissector forceps helped by the lateral and up and down movements performed by 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. 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 esophago-esophageal anastomosis was performed with 5-0 polydioxanone using a 3 mm transthoracic needle holder. The first esophago-esophageal 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 knotpusher. After two or three stitches on the posterior wall, a nasogastric tube was inserted.
through the mouth. A total of 7 to 10 single sutures were performed. 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, since 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 endotracheal tube. A technique to complete intracorporeal knots was developed but it was abandoned regarding its complexity and difficulty. We adopted extracorporeal knots that were simpler, faster and effective to accomplish esophageal anastomosis. Another difficulty was the intercostal hemorrhage caused during the manipulation of 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

Surgical procedure is summarized step-by-step in figure 2 and video 1. 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 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: i) to put the distal esophageal end close to the proximal esophageal end and ii) to include all the layers of the esophageal wall in the sutures. The first stitch, in particular, was the most difficult to perform, due to the lack of stability of the esophagus (Figure 2F). A nasogastric tube was inserted after the first two to three stitches, turning the anastomosis easier and faster to
perform (Figure 2I, J). However, the insertion of the nasogastric tube was again a challenging step, requiring an optimal coordination between both thoracoscopic and peroral operators. The anastomosis procedure was completed dominantly by transthoracic needle holder helped by peroral rotation of the esophagus. Extracorporeal knots were performed with a 3 mm knot-pusher inserted through the thoracoscope (Figure 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 with a range of 62 to 137 minutes. At the end of the procedure, the final aspect of the anastomosis was properly checked (Figure 2L). Additional stitches were performed as much as necessary. The manipulation of the instruments needs to be cautious because of the proximity with the intercostals vascular structures. After sacrifice 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 (Figure 3).
DISCUSSION

Thoracoscopic repair of EA includes obvious advantages like better visualization of the surgical field, less postoperative pain, better cosmesis and few 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 XXI century minimally invasive procedure. Although the first NOTES approach was a transvaginal procedure described by Decker in 1944 [11], the enthusiasm about this technique 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 included: i) reduction of general anesthesia use, ii) decrease hospitalization time and postoperative pain, iii) prevention of skin incision complications (wound infection and hernias), iv) increment of outpatient regimen, v) faster return of bowel function, vi) better cosmetic outcomes and vii) increase overall patient satisfaction [9]. Besides all these advantages, pure NOTES has still some limitations in the present.

Pure peroral approach might have some disadvantages like the extreme difficulty to create 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 - since 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 rout, triangulation and counter-traction 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.

Esophageal atresia can be an excellent congenital malformation candidate for peroral hybrid NOTES. At the present, the upper esophageal pouch is only used for the introduction of the nasogastric tube but in our opinion upper esophageal pouch could be potentiated as a route for the thoracic cavity. Rolanda et al 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 to perform this technique in a big animal model. In the present study, we demonstrated the feasibility to combine peroral and transthoracic routes to perform an esophago-esophageal anastomosis in rabbits. This animal model perfectly simulate 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 it happens in human newborns. In this work, we explored the prone position of the animal to amplify our field of work. 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, stating the advantage to easily access the mediastinum with the help of the gravity, to use lower CO₂ pressures and to decrease the time of procedure [10]. In thoracoscopic repair of EA different centers are using partial prone position of the patient with 30 to 45 degrees [4, 19] and a fourth port is sometimes applied to retract the lungs [4, 19]. A complete prone position may be more helpful than a partial one.

The great innovation of this study is the possibility to perform a 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 10mm trocar might be considered more invasive than 3 trocars of 5mm 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 telescopes 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 inconvenient 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 to grasper 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 gaster 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 in similar time than using 3 or 4 transthoracic trocars. This surgical technique, combining peroral and transthoracic approaches, demands a well synchronized performance between surgeon and first assistant to guarantee optimal results. While in thoracoscopy or laparoscopy the same surgeon performs all the movements with both hands, in hybrid NOTES it is needed to have an operator in each port. A good coordination between them is essential, permitting them to obtain synchronized movements as like as the hands of each operator belonged to the same surgeon. Our team 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.

The authors identified some limitations in the present study: i) tracheostomy to ventilate rabbits and ii) lack of a true EA with TEF, the most common type of EA. During our learning curve, we abandon 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 to perform 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 corpse 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 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 to perform an esophageal anastomosis combining single transthoracic port with peroral port in a rabbit model that simulates human newborn. This study provides several important insights to the translation for hybrid NOTES repair of human newborns with EA. We anticipate that in a near future, peroral route will replace, if not two, at least one transthoracic trocar.
REFERENCES


**LEGEND OF FIGURES**

**Figure 1**

Layout of the operating room. Monitor 1 was for the peroral operator; Monitor 2 was for Thoracoscopic operator.

**Figure 2**

Major steps executed during the protocol. Dissection was performed by transthoracic operator while peroral operator access esophageal lumen with a flexible endoscope, permitting him to take lateral movements and up (a) and down (b) movements. Complete esophageotomy was achieved by a peroral scissor (c) helped by a transthoracic grasper in which held the distal esophageal portion in the end of the section (d). After peroral operator grasped the distal section of the esophagus (e), transthoracic operator started the anastomosis with the first stitch (f), ended the extracorporeal knot with a knot-pusher (g). The excess wire was cut by a transthoracic scissors (h). 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). Anastomosis process was continued (k) until it was completed (l).

**Figure 3**

External (a) and internal (b) view of the esophageal anastomosis.
Table 1 - Pearls and pitfalls of the protocol identified by the group.

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<th>Pearls</th>
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<tr>
<td>Transthoracic trocar at the lower end of the right scapula</td>
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<td>Coordination between operators</td>
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<td>Peroral use of conventional 3 mm instruments</td>
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<td>Esophageal dissection helped by peroral endoscope</td>
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<td>Introduction of the nasogastric tube</td>
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<td>Intercostal vessels proximity to surgical maneuvers</td>
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