Innovations in the Surgical Management of Congenital Diaphragmatic Hernia

KuoJen Tsao, MD\textsuperscript{a,b,c,*}, Kevin P. Lally, MD, MS\textsuperscript{a,c}

KEYWORDS
- Congenital diaphragmatic hernia
- Minimally invasive surgery
- Tissue engineering
- Diaphragmatic patch

KEY POINTS
- The mortality for neonatal congenital diaphragmatic hernia has not improved in the last 15-25 years. Despite improved understandings in the pathophysiology, the overall survival is approximately 68%.
- Recent advances in neonatal congenital diaphragmatic hernia have focused on surgical approaches and diaphragmatic replacements. Both have attempted to reduce the morbidity associated with surgical repair of CDH.
- Better understanding of clinical outcomes requires a risk-stratified approach to analysis. This is dependent on a standardized classification of risk and disease severity.

OBJECTIVES
- Understand the surgical approaches to the repair of congenital diaphragmatic hernia as well as their associated morbidity.
- Understand the current options for diaphragmatic replacement.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) remains one of the most challenging neonatal diseases for pediatric surgeons and neonatologists. The spectrum of disease can range from asymptomatic, undiagnosed defects that present later in life to those with immediate respiratory distress that result in neonatal death. Despite the overwhelming interest and research in CDH, there has been minimal improvement in outcomes in the last 15 to 25 years since the adoption of delayed surgical repair with permissive hypercapnea and gentle ventilation.\textsuperscript{1}

Financial disclosures: None.
\textsuperscript{a} Department of Pediatric Surgery, The University of Texas School of Medicine at Houston, Houston, TX, USA; \textsuperscript{b} Department of Surgery, The University of Texas School of Medicine at Houston, Houston, TX, USA; \textsuperscript{c} The Children’s Memorial Hermann Hospital, Houston, TX, USA
\textsuperscript{*} Department of Pediatric Surgery, The University of Texas School of Medicine at Houston, 6431 Fannin Street, Suite 5.254, Houston, TX 77030.

E-mail address: kuojen.tsao@uth.tmc.edu

perinatology.theclinics.com
0095-5108/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
Until the late 1980s the overall survival rate was approximately 50%,\textsuperscript{2,3} with rates individual centers ranging between 20% and 70%.\textsuperscript{1,4} Today, survival has improved with a reported overall rate of 68%,\textsuperscript{5} while innovative therapies such as perfluorocarbon-induced lung growth\textsuperscript{6} and fetal tracheal occlusion\textsuperscript{7,8} continue to be evaluated. Innovations in the surgical treatment of CDH have focused on reduction in morbidity, specifically on surgical approaches and alternative diaphragmatic replacements. In addition, understanding the need for risk-adjustment analysis in rare diseases has enhanced the interpretation of clinical outcomes.

**SURGICAL APPROACH**

*Minimally Invasive Techniques*

The surgical repair of CDH has been traditionally performed via an open thoracic or abdominal approach. Laparotomy provides several advantages over thoracotomy, including easier reduction of intrathoracic viscera, ability to mobilize the posterior rim of diaphragm, easier management of intestinal rotational anomalies, and avoidance of thoracotomy-associated musculoskeletal sequelae. The vast majority of neonatal repairs for CDH are through a subcostal laparotomy (91%).\textsuperscript{9} However, the morbidity and respiratory sequelae of open repair of CDH remains a concern. In addition to the CDH-related effects of pulmonary hypoplasia and hypertension, reduction in abdominal and chest wall compliance after repair may exacerbate the pathophysiology of severe CDH. In hopes of minimizing the postoperative effects, surgeons have increasingly adopted a minimally invasive surgery (MIS) approach to the repair of CDH since Silen reported the first MIS repair of an adolescent Bochdalek-type CDH in 1995.\textsuperscript{10} Data from the Congenital Diaphragmatic Hernia Registry demonstrate that operative techniques include open abdominal and thoracic approaches as well as laparoscopic and thoracoscopic strategies, and that MIS techniques have been used in 20 of the 93 centers (21.5%).\textsuperscript{11} Comparative evidence between MIS and open approaches has been limited to single-institution experiences or retrospective analysis.\textsuperscript{11–17} Proponents of MIS tout benefits in cosmesis with smaller incisions, decreased postoperative pain, and possible improvements in postoperative pulmonary compliance, while minimizing complications of thoracotomy and laparotomy such as incisional hernias, chest wall deformities, musculoskeletal maladies, and adhesive intestinal obstruction.

The sensitivity of CDH infants to hypercapnea and acidosis has drawn concerns regarding the utilization of MIS, for 2 major reasons: (1) CDH neonates may absorb the CO\textsubscript{2} used for insufflation\textsuperscript{18,19} and (2) insufflation with CO\textsubscript{2} may raise intracavity pressures thus limiting venous return, end-organ perfusion, and tidal volume. The combination of CDH-related pulmonary hypoplasia, pulmonary hypertension, and labile pulmonary vascular reactivity may compromise physiology in the operating room. Although increases in CO\textsubscript{2} absorption during MIS are generally well tolerated in infants, CDH neonates specifically demonstrate greater changes in end-tidal CO\textsubscript{2} (EtCO\textsubscript{2}) and impaired elimination of CO\textsubscript{2} during thoracoscopy and laparoscopy.\textsuperscript{20,21} Hypercapnea and the associated acidosis may result in increased pulmonary shunting. Because of these concerns, the selection criteria for infants undergoing MIS repairs should be carefully scrutinized. Centers that perform thoracoscopic CDH repairs have advocated for stringent intraoperative monitoring of EtCO\textsubscript{2} and arterial partial pressure of CO\textsubscript{2}.\textsuperscript{22}

With increased surgeon experience and improved understanding of the physiology of MIS and CDH repair, selection criteria for patients have also expanded. Historically, MIS approaches were reserved for stable infants with anticipated small defects. Using anatomic markers such as stomach herniation, surgeons have attempted to predict
which defects are amenable to MIS repairs.\textsuperscript{23} Initially the presence of the nasogastric tube within the abdomen on radiograph, suggesting an intact esophageal hiatus with stomach and liver in the abdomen as well as minimal respiratory compromise (peak inspiratory pressures [PIP] <24 mm Hg), were thought to be associated with successful thoracoscopic repair. Gourlay and colleagues\textsuperscript{24} reported 95% success rates with thoracoscopic repair when patients demonstrated absence of significant congenital cardiac anomaly, absence of preoperative extracorporeal membrane oxygenation therapy (ECMO), PIP 26 cm H\textsubscript{2}O or less, and Oxygenation Index 5 or less on the day of surgery. Today, the application of MIS has expanded to those infants with more severe sequelae of CDH. For example, infants requiring preoperative ECMO have undergone successful repair with a MIS approach.\textsuperscript{18,25} In addition, large defects that require patch repairs\textsuperscript{18,24,26} and right-sided defects are no longer contraindications to MIS.\textsuperscript{27}

Despite demonstration of the ability to perform the repair via an MIS approach, little assessment of short-term and long-term outcomes regarding the durability and recurrence rates for MIS techniques has been performed. Early recurrence rates have been reported to be as high as 23% to 33% from individual centers,\textsuperscript{13,15} while the recurrence rate for thoracoscopic repairs was 16.1% compared with 4.9% for open repairs in one study (relative risk 3.21; 95% confidence interval [CI] 1.11–9.29). In a recent review of the CDH Registry, MIS repairs were performed in only 3.4% infants with CDH, with a significantly higher in-hospital recurrence rate for MIS repairs (7.9% vs 2.7%, \textit{P}<.05). Thoracoscopic CDH repairs had the highest rate of recurrence, at 8.8%. The odds ratio (OR) for recurrence with MIS was 3.59 (95% CI 1.92–6.71) after adjusting for gestational age, birth weight, patch repair, and need for ECMO. A meta-analysis of neonatal MIS repair for CDH identified only 3 relevant studies with a total of 143 patients.\textsuperscript{16} Thus, the current evidence is subject to the pitfalls of retrospective studies, that is, selection bias and inadequate follow-up, and our understanding of long-term outcomes remains limited.

\textbf{Robotic Techniques}

Robotic repair of congenital diaphragmatic anomalies have been demonstrated to be feasible and safe.\textsuperscript{28–30} Advances in 5-mm robotic instrumentation in the last 10 years have allowed operative access to neonatal patients. Proponents of robotic CDH repair tout the increased degrees of freedom of the articulating instruments for suturing. Bochdalek-type and Morgagni-type hernias have been repaired with robotic assistance via a laparoscopic or thoracoscopic approach.\textsuperscript{30} Slater and Meehan\textsuperscript{30} reported their experience with robotic repairs of diaphragmatic anomalies in 8 patients with an average weight of 3.6 kg (range 2.2–10.5 kg) including 5 patients with Bochdalek-type hernias. Two patients required conversion to conventional MIS techniques and one patient developed a recurrence, with an average follow-up of 18 months. Although the thoracic approach was preferred, the surgeons suggested that an abdominal approach may be better for smaller newborns less than 2.5 kg because of the increased space required for the articulating instruments. Although the long-term outcomes remain unclear, continued improvements in technology provide promise for robotic surgery for CDH.

\textbf{DIAPHRAGMATIC REPLACEMENTS}

Repair of large diaphragmatic hernias is a surgical challenge for pediatric surgeons. According the CDH Registry, 48.3% of infants undergoing repair require a patch.\textsuperscript{31} When primary repair is not possible, diaphragmatic replacement with a prosthetic
patch or autologous tissue becomes necessary. Comparative studies between patch and no-patch repairs have consistently shown increased morbidity and mortality in the patch groups, most likely due to the underlying defect size and the associated severity of the pulmonary hypoplasia. In many clinical research studies, patch repair is used as a surrogate for defect size and disease severity (ie, larger defect leads to increased severity of respiratory disease).  

The options for patches consisting of nonabsorbable synthetic or absorbable biosynthetic materials have increased over the last 20 years (Box 1).

**Nonabsorbable Synthetic Patches**

Nonbiodegradable materials such as polytetrafluoroethylene (PTFE or Gore-Tex) or composite-mesh polypropylene (Marlex) are routinely used to provide a tension-free repair of CDH. Synthetic patches are commonly used for several reasons: (1) they are easily sized to fit the diaphragmatic defect, (2) less tissue dissection and mobilization is required, thus reducing the risk of hemorrhage when repair is performed on ECMO, and (3) they can be used immediately and require minimal preparation time. Synthetic patches represent the majority of the mesh diaphragmatic replacements used in neonates with large CDH.

There are several disadvantages to synthetic patches for the repair of CDH. The overall recurrence rate has been reported to be as high as 50%. Recurrence with PTFE appears to be bimodal, with an early peak in the first months after repair and late recurrences years later. Early recurrences are most likely due to inadequate tissue adhesion or scarring, as may be seen with large defects with small or incomplete muscular rim that requires anchoring to the ribs or esophagus. PTFE tends to scar and shrink diaphragm over time, which may lead to late recurrences in the growing child. Several techniques have been described in an effort to prevent CDH recurrence. Loff and colleagues constructed a cone-shaped, double-fixed PTFE

---

**Box 1**

**Diaphragm replacements**

<table>
<thead>
<tr>
<th>Nonabsorbable synthetic patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polytetrafluoroethylene (PTFE) (Gore-Tex)</td>
</tr>
<tr>
<td>PTFE and polypropylene (Marlex)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absorbable biosynthetic patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine intestinal submucosa (Surgisis)</td>
</tr>
<tr>
<td>Porcine dermal collagen (Permacol)</td>
</tr>
<tr>
<td>Human cadaveric dermis (AlloDerm)</td>
</tr>
<tr>
<td>Fetal bovine dermal collagen (Surgimend)</td>
</tr>
<tr>
<td>Polylactic-co-glycolic acid (PLGA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autologous tissue patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse latissimus dorsi muscle</td>
</tr>
<tr>
<td>Serratus anterior muscle</td>
</tr>
<tr>
<td>Internal oblique/transversus abdominis muscles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue-engineered patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid, stem cell–derived muscle</td>
</tr>
</tbody>
</table>
patch to allow the patch to expand over time. As a result, the recurrence rate decreased from 46% to 9% in the first year after repair. Others have used a mesh plug and patch in the setting of recurrent CDH repair, with similar results. Riehle and colleagues described use of a double-sided composite patch consisting of PTFE on one side and type-1 monofilament, macroporous polypropylene (Marlex) on the other. Using a pledgeted, nonabsorbable running suture for fixation, recurrence occurred in 1 of 46 patients with a mean follow-up of 49 months.

Although prosthetic patches seem to be a good initial solution, long-term complications appear to be increased with nonabsorbable materials. Patches, such as PTFE, that are anchored to the chest wall can potentially produce a tethering point and may contribute to pectus-type deformities. Other investigators have described an increased incidence of bowel obstruction, need for splenectomy, patch infections, and abdominal wall deformities.

**Absorbable Biosynthetic Patches**

In efforts to avoid the aforementioned complications related to synthetic patches, alternatives to prosthetic materials have been introduced. Absorbable biosynthetic materials offer lower risks of infection and the ability to grow with the patient. Surgisis is an acellular, bioengineered porcine intestinal submucosal matrix that consists of a type-I collagen lattice with embedded growth factors. This non–cross-linked biological matrix is absorbed into the tissue bed, and promotes fibroblast migration and cellular differentiation. First used to repair incisional, inguinal, and paraesophageal hernias, Surgisis has been widely used for the repair of CDH. Despite the demonstrated engraftment and neovascularization, recurrence rates for Surgisis appear to be similar when compared with Gore-Tex. However, Surgisis demonstrated a higher rate of small bowel obstruction (31% for Surgisis vs 9% for Gore-Tex).

Permacol is an acellular sheet of porcine dermal collagen consisting of cross-linked lysine and hydroxylysine residues within the collagen fibers that promote a minimal inflammatory process. Theoretically, with inflammation similar to that of wound healing the neodiaphragm is more pliable and, subsequently, less prone to recurrence. In a study by Mitchell and colleagues, there were no recurrences observed with Permacol in 8 patients with a median follow-up of 20 months, whereas recurrences were noted in 2% of patients with primary repair and 28% of diaphragms reconstructed with Gore-Tex.

Several other biosynthetic patches have been developed and used in the repair of CDH. AlloDerm is an acellular human cadaveric dermis that is cross-linked for rapid revascularization. This patch requires a 2-step rehydration process. Animal studies have demonstrated revascularization and cell repopulation within 1 month. Surgimend is an acellular fetal bovine dermal collagen. Consisting of interwoven collagen, Surgimend may promote increased type-III collagen of fetal origin that contributes to scarless wound healing. Because there is no cross-linking there is an increased collagen resistance to collagenase, leading to greater durability. Polylactic-co-glycolic acid (PLGA) is a collagen scaffold that promotes neovascularization and autologous tissue regeneration. Animal studies have demonstrated ingrowth of fibroblasts, resulting in a thicker neodiaphragm.

Despite the theoretical advantages, absorbable biosynthetic patches remain imperfect. Materials such as Surgisis have demonstrated thinning and incomplete muscular ingrowth. Vascular ingrowth may be difficult, especially in large defects where native diaphragmatic muscle is absent. Albeit from different causes, biosynthetic patches are prone to recurrent hernia formation, much like nonabsorbable patches. In addition, organ adherence, often to the small bowel, spleen, or liver, appears to be required for neovascularization. Consequently, biological patches may also be associated
with adhesive bowel obstruction. Because of these many disadvantages, biosynthetic patches have fallen out of favor with many surgeons.

**Autologous Tissue Patches**

Persistent complications with synthetic and biosynthetic patches have prompted some surgeons to advocate for primary repair with autologous muscle flaps, or staged reconstruction of large diaphragmatic defects with an initial synthetic patch followed by an autologous muscle flap. Muscle flaps offer the advantage of using a vascularized tissue that will grow with the infant.

Several different abdominal muscle flaps have been described as a diaphragmatic replacement. In 1962, Meeker and Snyder first described using anterior abdominal wall for repair of a CDH. In 1971, Simpson and Gossage described use of a split abdominal wall muscle flap to repair a large defect in a 1-day-old neonate. Scaife and colleagues described using a split abdominal muscle flap of the internal oblique and transversus abdominis muscles for primary repair of large diaphragmatic hernias. Using a lower abdominal incision the transversus abdominis was utilized to repair a CDH, with complete agenesis of the diaphragm on ECMO. This approach appears to have minimized the hemorrhagic risk while repairing a CDH on ECMO, owing to the avascular dissection plane between the muscle layers.

Chest wall muscles have also been used to repair diaphragmatic hernia. The reverse latissimus dorsi muscle flap was first described by Bianchi and colleagues in 1983. Based on the lumbar perforating blood vessels, the reverse latissimus dorsi muscle provides a wide pedicle for a tension-free repair. For very large defects, such as agenesis of the diaphragm, combined use of the latissimus dorsi and serratus anterior muscles has been described. Although autologous muscle flaps are vascularized and tend to grow with the child, these diaphragmatic reconstructions with latissimus dorsi/serratus muscle flaps are typically small and have demonstrated atrophy over time because of denervation of the graft. In addition, the lack of innervation prevents the natural physiologic movement of the muscle flap. As a result, some surgeons have advocated using the reverse latissimus dorsi flap with a microneural anastomosis of the phrenic nerve to the thoracodorsal nerve, to prevent muscle atrophy and to allow physiologic muscle movement. Sydorak and colleagues described their initial experience with this technique in 7 infants with CDH. At a median age of 24 months, the investigators demonstrated fluoroscopic evidence of nonparadoxic neodiaphragmatic motion resulting from phrenic nerve innervation, including evidence of phrenic nerve conduction.

The disadvantage with using local muscle flaps is the associated deformity of the body wall. Consequently, muscle flaps have been primarily reserved for reconstruction in the setting of recurrent CDH. Although the risk of infection is low and growth is observed with autologous tissue, recurrence is a risk, attributable to atrophy of a denervated muscle flap.

**Tissue-Engineered Patches**

As may be seen from the foregoing discussion, the ideal diaphragmatic replacement remains elusive in the operative treatment of CDH. Advances in regenerative medicine may provide alternatives for diaphragmatic repair. For example, tissue-engineered muscle may provide a patch of functional skeletal muscle that may not atrophy and has minimal risk of infection. Although the supporting 3-dimensional scaffold is a key component of tissue engineering, skeletal muscle regeneration relies on a cell source with myogenic potential. Amniotic fluid–derived stem cells may be a safe and abundant source of cells with myogenic potential. Collected at the
time of amniocentesis, amniotic stem cells could be used to engineer a muscular patch to be used during postnatal repair. Fuchs and colleagues have developed a fetal tissue–based diaphragmatic construct by using autologous tendon engineered from mesenchymal amniocytes. Improved mechanical and functional outcomes offer promise for clinical application in the near future when compared with acellular bioprosthetic patches in preclinical studies.

**RISK STRATIFICATION FOR CDH**

Rare diseases, such as CDH, present major challenges in clinical care as well as in interpretation of clinical outcomes. Because of the wide spectrum of disease severity, most centers have highly variable experience in the severity of CDH from year to year with most advanced therapies. As such, clinical evidence has been limited in quality and only to broad conclusions.

The size of the diaphragmatic defect has been associated with severity of disease. The Congenital Diaphragmatic Hernia Study Group (CDHSG) classified CDH based on the size of the defect and type of repair: primary repairs, repairs with patch that were not agenesis of the diaphragm, and agenesis of the diaphragm. The overall mortality for patients with agenesis of the diaphragm was 43%, with an OR of 14.07 (95% CI 10.35–19.13) in comparison with primarily repaired defects. The association between defect size and disease severity has prompted development of a universal grading system that uses a diagrammatic schema to define CDH defect size. The 4 classifications range from small defects that could be repaired primarily to total diaphragmatic agenesis based on intraoperative findings (Fig. 1). Using other variables of comorbidity and disease

---

**Fig. 1.** Classification of congenital diaphragmatic hernia based on intraoperative defect size. Diagrams are drawn with the diaphragmatic defect on the patient’s left from an abdominal approach. (From Tsao K, Lally KP. The Congenital Diaphragmatic Hernia Study Group: a voluntary international registry. Semin Pediatr Surg 2008;17:90–7. CDH website. Available at: http://utsurg.uth.tmc.edu/pedisurgery/cdhsg/index.html. Accessed April 13, 2012.)
severity, the CDHSG is attempting to provide an evidence-based risk-stratification classification of CDH. This issue is particularly prudent when innovative therapies are introduced, so as to ensure appropriate comparative analysis.

SUMMARY

Despite improvements in survival and major paradigm shifts in management, consensus treatment and management of infants with CDH remain elusive. Quality clinical evidence to support many modalities is limited. Most outcomes data are reported from either single-center experiences, hospital databases, or network registries. There remain a limited number of prospective controlled clinical trials that examine various interventions for infants with CDH. As such, the evidence to support innovations in surgical treatment of CDH suffers from low-quality clinical evidence, often attributable to compromises in study design and limitations of sample size. According to the CDH Registry, the average number of CDH infants seen per center is less than 10 per year. Even high-volume centers may have limited experience with novel treatment modalities because of the broad spectrum of disease. Although many advances in the treatment of CDH demonstrate promise, outcomes data for novel CDH therapies should be carefully evaluated, with an understanding of risk stratification, before the adoption of any new treatment.

REFERENCES


