Eventration of Diaphragm

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Soichi Shibuya and Paolo De Coppi

Eventration of the diaphragm is defined as an abnormal elevation of the diaphragm toward the pleural cavity. Congenital eventration is rare, with an incidence of <1 per 10,000 births. It is more often limited to the left diaphragm and thought to be due to a defective embryological development of the diaphragmatic muscle at level of the fibers or from lack of muscle innervation. Alternatively, it is defined as acquired secondary to phrenic nerve damage following a birth trauma or mediastinal surgery. Reports are highly variable, but phrenic nerve palsy is observed in perhaps up to 10–12% of children undergoing cardiac surgery.

Eventration can impair respiratory function by suppressing expansion of the lung, according to the severity of the elevation. In the congenital form, eventration may present with symptoms of respiratory distress requiring support with mechanical ventilation. Differential diagnosis includes congenital diaphragmatic hernia with a sac. In the acquired form, the respiratory symptoms are nonspecific, such as cough, sputum expectoration, wheezing, tachypnea, and recurrent infections. Most patients present with only mild symptoms or may even be asymptomatic and detected only via an incidental finding on chest X-Ray. However, a minority of patients will develop severe respiratory distress, requiring ventilatory support. Moreover, the extra space connected to the abdominal cavity allows migration of the abdominal organs, such as the stomach and the small intestine, and occasionally causes gastrointestinal symptoms. Similarly to the respiratory symptoms, the gastrointestinal symptoms are normally broad and tend to be mild, including nausea, vomiting, and weight loss. However, there is a certain chance that the migrated gut suddenly becomes strangled, leading to an acute abdomen that requires emergency surgical attention. In addition, as irregular movement of the diaphragm may cause discoordination of sucking and breathing, neonates with diaphragmatic eventration sometimes suffer feeding intolerance that results in failure to thrive.

Physiology

In the normal physiologic state, contraction of the skeletal muscles comprising the diaphragm flattens its domed shape, generating a negative pressure in the pleural cavity that triggers flow of air into the airway. This function synchronizes with expansion of the rib cage that is induced by relaxation of the internal intercostal muscles and contraction of the external intercostal muscles, which likewise promotes reduction of the pleural pressure. On the other hand, in the setting of diaphragmatic eventration, decreasing intrapleural pressure induces passive elevation of the floppy diaphragm on the affected side when inspiration starts, while the contralateral diaphragm contracts to be flattened, resulting in *paradoxical movement* of the diaphragm. The imbalance of the pressure between the two pleural spaces also gives rise to mediastinal shift toward the healthy side drawn by the negative pressure, which can potentially affect hemodynamics if severe. Although it is rare, if both sides are severely affected, it becomes difficult to create a sufficient negative pressure, and the patient is likely to be subject to ventilatory support.

Etiology

The fundamental pathology of diaphragmatic eventration is a loss of muscular tension of the diaphragm. Two mechanisms have been known as the major cause of the laxity of the diaphragm—one is impairment of the skeletal muscles, the

S. Shibuya · P. De Coppi (✉)
Stem Cell and Regenerative Medicine Section, Developmental Biology and Cancer Research & Teaching Department, Zayed Centre for Research into Rare Disease in Children, Great Ormond Street Institute of Child Health, University College London, London, UK
e-mail: s.shibuya@ucl.ac.uk; p.decoppi@ucl.ac.uk

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other is diminished muscle contractility due to neurological dysfunction. The former is essentially a congenital condition resulting from impaired muscularization of mesodermal cells during diaphragm development. Associations with genetic disorders, including Beckwith–Wiedemann Syndrome, trisomy 13, 15, or 18, as well as congenital cytomegalovirus infection, have been reported. Several other pathologies, such as Duchenne muscular dystrophy and spinal muscular atrophy, also cause progressive wasting of the diaphragm after birth. On the other hand, neurological dysfunction usually occurs secondary to phrenic nerve injury associated with chest surgery or birth trauma. It also occasionally develops as a result of acquired neurological conditions like Guillain–Barré syndrome and Parsonage Turner syndrome.

The diaphragm develops as a result of the fusion of several primitive components, namely the septum transversum, the dorsal foregut mesentery, and the pleuroperitoneal folds. The septum transversum represents the major component of the diaphragm and is considered to give rise to the central tendon, which covers the central part of the diaphragmatic dome. It originally emerges as a thick mesodermal plate cranial to the stalk of the yolk sac, and extends posterolaterally to form the partition between the pleural and peritoneal cavities. However, the dorsal expansion of the septum transversum halts in the vicinity of the gut tube, leaving an opening on each side. These gaps, called pleural canals, later close as a consequence of the fusion of the septum transversum with the foregut mesentery and the pleuroperitoneal folds. The dorsal foregut mesentery, comprised of primitive mesenchyme surrounding the dorsal part of the esophagus, constructs the median portion of the diaphragm, subsequently giving rise to the crura of diaphragm.

The pleuroperitoneal folds, also called pleuroperitoneal membrane, are a pair of pyramidal-shaped protrusions arising from the dorsolateral part of the body cavity at the caudal border of the pleural cavity. The pleuroperitoneal folds extend ventromedially to fuse with the dorsal foregut mesentery and the dorsal part of the septum transversum. These have been postulated to be responsible for the regulation of muscle and nerve cell migration and morphogenesis of the diaphragm. Despite their critical role in diaphragm development, in the end the pleuroperitoneal folds comprise only a small portion of the developed diaphragm. The fusion of the rudiments normally occurs during 5–8 weeks of gestation, consequently completing separation of the embryonic body cavity into the pleural and peritoneal cavities. Failure in this process leaves a defect in the diaphragm, resulting in congenital diaphragmatic hernia, of which type is classified according to the location of defect. Simultaneously, with the formation of the primitive partition, migration of muscle precursor cells takes place, eventually turning the nascent, membranous diaphragm into a muscular, dome-shaped structure. The muscle progenitor cells have the origin in the somite, more specifically the hypaxial (ventrolateral) dermomyotome, which is compartmentalized as a result of specification of the paraxial mesoderm, and emigrate to the pleuroperitoneal folds.

Once the pleuroperitoneal folds are reached, the muscle progenitors initiate myogenesis, the process of differentiation and integration into multinucleate myofibers. Like the other types of skeletal muscles, diaphragm progenitor cells initially express the transcription factors Pax3 and Pax7, and subsequently give rise to myoblasts that express Myf5 and MyoD, eventually fusing to form multinucleated myofibers. Myofibers develop first in the pleuroperitoneal folds and spread toward the septum transversum along with the expansion of the pleuroperitoneal folds. Developed myoblasts structure the costal and crural muscles, which support the central tendon and function to trigger the breathing movement. The contiguous body wall also shows muscular ingrowth toward the central, forming the peripheral part of the diaphragm. This muscularization process continues over 8–10 weeks of gestation.

Although it has yet to be revealed, disruption in the process of migration and maturation of muscle progenitor cells has been considered to be the cause of congenital eventration. Histological studies of diaphragmatic eventration patients support this hypothesis, showing fibrous dysplasia in the diaphragmatic muscle. The dysplasia is usually observed in the central part of the diaphragm rather than the lateral part where the muscle progenitor cells depart, indicating incomplete migration of the muscle progenitor cells. Interestingly, there has been literature based on studies of mouse embryo, reporting the existence of the muscle progenitor cells in the central tendon of the developing diaphragm, which later disappear from the area that lacks innervation by the phrenic nerve. This observation has led to the hypothesis that phrenic nerve innervation is required for maintenance and adaptation of the myoblasts. Identification of the signals helping the interaction among the components would be an interesting avenue for future research into the pathogenesis of diaphragmatic eventration.

The contraction of diaphragm muscle is dependent on the stimuli from the phrenic nerves that exist on the right and left side separately innervating each hemi-diaphragm on the corresponding side. The phrenic nerves consist of nerve fibers originating from the anterior rami of the C3, C4, and C5 nerve roots, and descends parallel and close to the pericardial sac, eventually spreading branches to the pleural aspect of the diaphragm to innervate myofibers of the crural and costal muscles. Development of the phrenic nerves begins at

5 weeks of gestation. The nerves originating from the cervical spinal segments grow toward the septum transversum passing through the pleuropericardial membrane, and thus, the phrenic nerves lie in the fibrous pericardium. In addition to motor nerve fibers, they also include sensory and sympathetic nerve fibers, providing touch and pain sensory innervation to the diaphragm as well as the mediastinal pleura. This sensory innervation explains the mechanism of Kehr's sign: a referred pain that arises around the tip of the shoulder when a pain signal from the phrenic nerve is erroneously triggered by irritation of the diaphragm. Because of the long and unique routes they take, the phrenic nerves are prone to injury during thoracic surgery. Loss of motor nerve stimulation due to phrenic nerve injury causes paralysis of the muscular part of the diaphragm. Therefore, such type of eventration is also referred to as diaphragmatic paralysis or diaphragmatic dysfunction. In the context of pediatrics, cardiac surgery for congenital heart disease is the commonest cause of phrenic nerve injury. The related occurrence has been reported to be up to around 10%, with higher incidences in Blalock–Taussig shunt, Tetralogy of Fallot repair, arterial switch operation, ventricular septal defect repair, Fontan procedure, and bidirectional Glenn procedure. It has been also reported that application of topical ice for cardiac cooling is associated with an increased risk of diaphragm paralysis. This form of diaphragmatic eventration more frequently occurs on the left side, which may be explained by the course of the left phrenic nerve, as it is more vulnerable to be involved in the surgical field during complex procedures. Postoperative diaphragmatic eventration tends to complicate the recovery of the patients after surgery for congenital heart disease, resulting in prolonged dependency on ventilatory support and delayed enteral nutrition. This in turn leads to prolonged hospital stays and higher costs. Other than heart surgery, damage to the phrenic nerve can occur associated with lung surgery and mediastinal surgery, such as pulmonary lobectomy and resection of mediastinal tumor. Although rare in children, it is worth remembering that neck surgery also harbors a risk of phrenic nerve injury.

Another common cause of acquired diaphragmatic eventration in the pediatric population is birth trauma involving phrenic nerve injury, commonly associated with a difficult vaginal delivery. In the setting of shoulder dystocia where the anterior shoulder of the newborn is trapped by the mother's pubis while the head is already delivered, overstretching of the baby's neck and shoulder can presumably result in injury to the cervical spinal nerves, including the brachial plexus. It has been reported to occur in 1–2 per 1000 births, with an increased incidence in larger babies, diabetic pregnancies, and maternal obesity. The upper brachial plexus (C5, C6, C7) is the area that is typically damaged by birth trauma, of which characteristic manifestations include Erb's palsy. Although damage to the higher cervical nerves (C3, C4) is relatively rare, neonates suffering brachial plexus injury warrant a careful examination with consideration of the possibility of concomitant phrenic nerve injury. Such newborns present breathing difficulty soon after birth, which potentially requires urgent resuscitation and ventilatory support. It has been reported that three quarters of cases with birth trauma-related phrenic nerve injury accompany branchial plexus injury. Finally, other causes of diaphragmatic eventration include compression or invasion by a mass lesion involving the phrenic nerve, even though direct physical injury does not exist. In such cases, symptoms are reversible, and extraction of the primal factor is usually the definitive treatment. Some cases remain symptomatic even after the removal of the lesion, indicating necessity of intervention.

Diagnosis

Physical examination can demonstrate decreased breath sounds on the affected side but will need validation with 2-view chest radiographs. Diaphragmatic eventration is typically suspected first from abnormal findings on a chest radiograph representing an elevated hemi-diaphragm. In a neutral position (between full inspiration and full expiration) the diaphragm is located at the sixth rib and the right hemidiaphragm is slightly higher than the left. Practically, the vertex position of the hemi-diaphragm more than two ribs higher than the contralateral counterpart has been considered to be abnormal. The frontal radiograph may show a double diaphragmatic contour, which can be confirmed on the lateral projection. Additional modalities are recommended to rule out other conditions may show similar findings, such as congenital diaphragmatic hernia, atelectasis, pulmonary mass lesion, and subphrenic effusion or abscess. Fluoroscopy has been for many years the gold standard for definitive diagnosis of diaphragmatic eventration. The paradoxical movement of the diaphragm is characteristic of diaphragmatic eventration and a synchronized mediastinal shift also can be observed. Where possible, forced sniffing helps to demonstrate the findings more clearly. A barium swallow can be useful to examine migration of the gastrointestinal tract and predict the existence of malrotation and volvulus. Ultrasound (US) has become the imaging test of choice since it can investigate the diaphragmatic movement in real time without radiation. Moreover, it can be used to measure the change in the thickness of the diaphragm during respiration, the direction of diaphragm movement, and the amplitude of excursion (>4 mm) representing the functionality of muscle contraction. CT and MRI are also useful for differential diagnosis

and screening for the primary cause of the diaphragm dysfunction. Careful review of CT or MRI angiography is important especially in patients associated with congenital heart disease to predict the abnormal anatomy of the vasculature, which may affect the operative procedure. Prenatal diagnosis of diaphragmatic eventration has been easier as a result of improved imaging resolution and technique. US and MRI are commonly used as the means of prenatal examination and it is even possible to detect paradoxical movement of the diaphragm in fetuses. Although distinguishing between diaphragmatic eventration and congenital diaphragmatic hernia with a sac is difficult, it has been suggested that a smooth convex interface between the herniated contents and lung on US or MRI is indicative of congenital diaphragmatic hernia with a sac rather than diaphragmatic eventration. In addition, lung function test combined with phrenic nerve stimulation is an option to assess the activity of the diapgragm but rarely adopted to children hampered by the technical complexity and invasive nature of the test.

Surgical Treatment

The severity of symptoms of congenital diaphragmatic eventration varies depending on the area of the affected part and it is yet unclear if there is a possibility of spontaneous improvement as the patient grows. Eventrations that are asymptomatic or associated with mild symptoms should be conservatively managed. However, surgery should be considered once patients present sign of deterioration. In neonates, a severe elevation (above the fourth intercostal space) can compress the lung and thwart postnatal lung growth; thus, it is recommended to be surgically repaired, even if the patient does not present with significant symptoms. In contrast to congenital diaphragmatic eventration, diaphragmatic paralysis due to phrenic nerve injury has a greater chance of spontaneous resolution often within a few weeks. However, if the symptoms continue over a month, surgical intervention is warranted.

Plication of the diaphragm is the standard choice of surgical treatment. If both sides are severely paralyzed, there is little chance of restoration of the diaphragmatic function and permanent ventilatory support might be required, though a few alternative options, such as phrenic nerve stimulation and intercostal nerve transfer, are being developed.

The main goal of the diaphragmatic plication is to fix the diaphragm in the normal position and restore moderate tension. The unique anatomical location of the diaphragm allows access through both the thoracic and abdominal cavity, leading to a variation in the surgical approach. The surgical techniques can be categorized according to the access route (trans-thoracic or trans-abdominal) and whether it is minimally invasive or open. Owing to the heterogeneity and relative infrequency of the disease, there is no strong consensus on the choice of surgery; therefore the decision is usually left to the preference and experience of the surgeon. Nevertheless, there are some factors that deserve consideration. In general, trans-thoracic approach tends to be preferred for right-sided cases because of relative accessibility compared to the trans-abdominal approach, which requires mobilization of the liver. Moreover, the trans-thoracic approach is considered to have less chance of bowel injury and postoperative bowel obstruction. However, respiratory deterioration associated with compression of the lung during the surgery can be a problem for patients in an unstable respiratory state. Unlike congenital diaphragmatic hernia, whereby the lung on the affected side is hypoplastic and rarely obstructs the operative field, the lung in diaphragmatic eventration tends to be mature so that single lung ventilation is often required. Moreover, if the patient has undergone surgery for congenital heart disease, postoperative adhesions in the chest cavity can be an issue, making the approach to the diaphragm complicated. For these reasons, our preference is to use a laparoscopic approach for the right-side eventration, since the simple maneuver of detaching the falciform ligament would leave enough space to safely plicate the diaphragm. Moreover, a trans-abdominal approach is also preferable for patients in unstable condition after cardiac surgery. We also argue that the trans-abdominal approach can provide better visibility of the entire diaphragm. This is important to achieve firm suturing including sufficient amount of the muscular diaphragm in the lateral part, while the lateral edge of the diaphragm tends to be too deep to reach through thoracic cavity. Although substantive evidence on its efficacy does not exist, Minimally Invasive Surgery (MIS) is generally considered to be beneficial in terms of reduction in operative stress and better visualization. Thoracoscopy is especially advantageous over open thoracotomy by sparing the intercostal muscles, which contribute to the expansion capacity of the rib cage, consequently preserving the respiratory function. As long as the patient's condition allows, the authors always aim to use MIS and the laparoscopic approach is especially favored. One of the reasons is that pneumoperitoneum can facilitate appreciation of the shape of the entire diaphragm by letting it protrude into the chest cavity, whereas pneumothorax during thoracoscopy flattens the diaphragm. In this setting, it is easy to grasp the vertex of the diaphragm. By pulling it caudally, the edge of the muscular part of the peripheral diaphragm, where stitches should be placed, can be readily delineated, enabling appropriate plication. Although mobilization of the liver is mandatory in right-sided plication, in our experience it has never been problematic, as separating the falciform ligament can provide enough space.

In thoracoscopic plication, three ports through the 4th or 5th intercostal space are commonly used, while an extra trocar is occasionally added for pushing the diaphragm caudally to maintain the operative field. In case the apex of the ele-

vated diaphragm is very high, higher port positions may be chosen to obtain better visibility; but if too high, the working angles of the devices may be compromised. Pneumothorax with CO_2 insufflation at 4–6 mmH_2O is usually sufficient to suppress expansion of the lung and prevent the diaphragm from bulging in the chest cavity. In cases where inflation of the lung is hard to control, single-lung ventilation can be effective, though it warrants expertise of the anesthetist for small infants. A chest tube may be useful to facilitate the proper lung expansion postoperatively but is optional.

Laparoscopic plication is usually performed using three ports, one at the umbilicus and two in the upper abdomen, of which positions are contingent on the side of eventration. As with thoracoscopic surgery, an extra trocar is usually useful to keep the abdominal organs away from the diaphragm. A slight reverse-Trendelenburg position also helps to create a space by moving the organs caudally. Right-side plication requires separation of the falciform ligament for exposure of the diaphragm. The position of trocars determines the working angles, which ultimately influences the efficiency of sutures; therefore, extra care must be taken when deciding the position (Fig. 79.1). Multiple variations of the plication technique—*reefing*, *folding*, and *pleating*—have been reported, although outcomes of each technique seem to be similar. Whichever technique is used, the most important thing is to include sufficient amount of the tissue, especially the lateral muscular part, in each suture. To that end, a thick non-absorbable suture is recommended. Multiple sutures are normally required to form an imbrication or an overlapping of the layers, which makes the plicated diaphragm more taut. Use of an endostapler device in laparoscopic plication has been reported as an alternative approach, but the evidence on the safety of removing part of the diaphragm has not been established and thus we do not recommend it. Upon plication, especially in the thoracoscopic approach, care must be taken not to injure the main branch of phrenic nerve, and it is also important to ensure there is not an involvement of the abdominal organs in the suture. Although it is relatively easy to see the abdominal organs through the thinned diaphragm, there can be adhesions between them due to continual migration. Using the trans-abdominal approach makes it easier to avoid this.

The outcome of surgery is generally satisfactory and those who have been preoperatively dependent on ventilatory support usually can be weaned off soon after. The potential complications vary according to the surgical approach. Pleural effusion, pneumonia, chylothorax, and pneumothorax are relatively common after a trans-thoracic approach, while the trans-abdominal approach is more frequently associated with abdominal organ injury and bowel obstruction. Recurrence is rare and likely to be technical. Some studies have reported a higher recurrence rate following the thoracic approach, but conflicting results also exist.

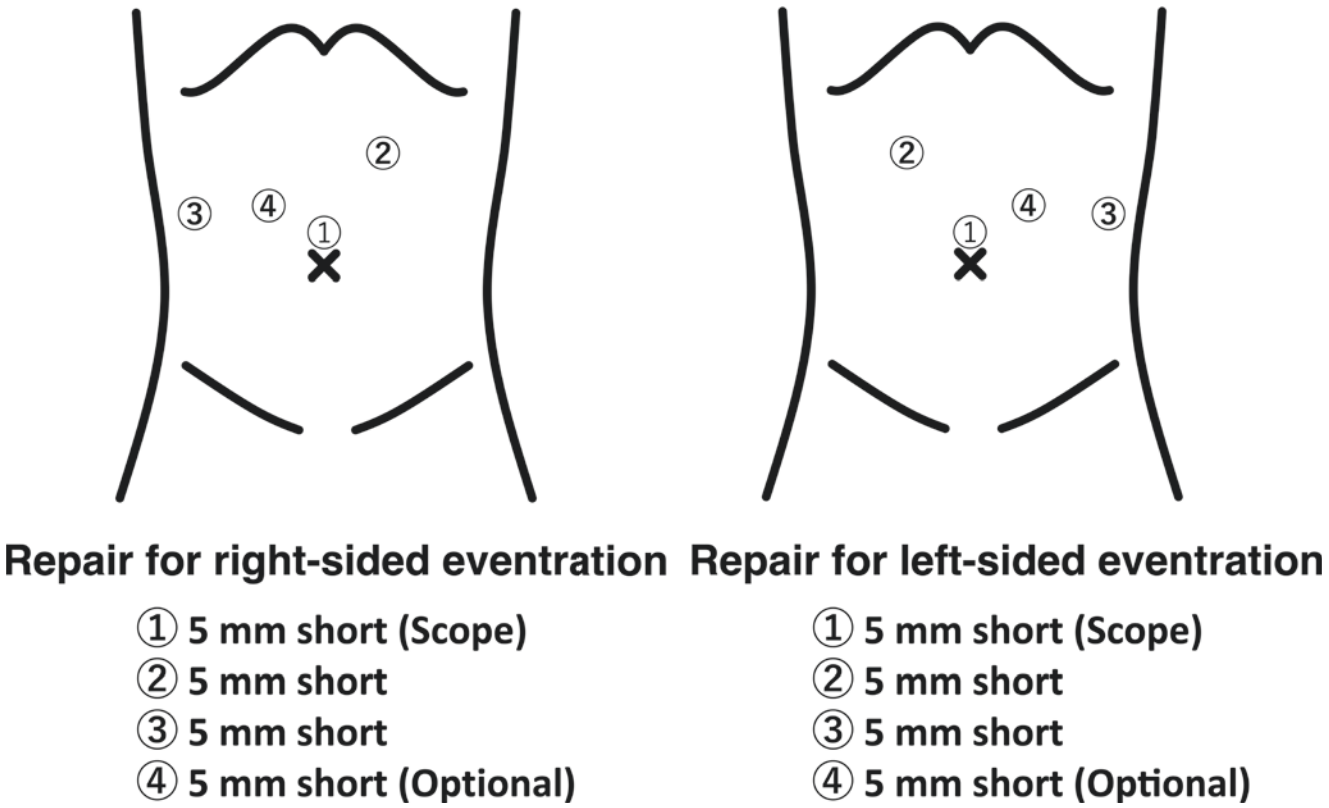

Fig. 79.1 Examples of port position

Trans-Thoracic Vs. Trans-Abdominal

Recently, we conducted a comparative study between transthoracic and trans-abdominal approaches alongside a literature review (Gupta et al. 2020). During the period between January 2004 and December 2018, 102 children underwent diaphragmatic plication either trans-thoracically (87%: Open = 86, MIS = 3) or trans-abdominally (13%: Open = 4, MIS = 9) in our center. Besides the number of recurrences, the position of the diaphragm by chest X-ray were compared before and after plication as a measure of improvement of diaphragmatic position. Interestingly, patients after trans-abdominal plication showed significantly greater improvement compared to the trans-thoracic approach (Median: 2 rib levels vs. 1.5 rib levels; $p = 0.04$). This result supports the idea that a better visibility of the entire diaphragm in the trans-abdominal approach is conducive to achieving sufficient plication. Although the following period was not matched and statistical significance was not shown by Cox regression analysis, none of the 13 patients repaired by trans-abdominal approach experienced short-term recurrence, whereas 16 (18.0%) recurred after trans-thoracic plication. We identified 4 other studies comparing the recurrence between trans-thoracic and trans-abdominal approach and evaluated risk difference using random effect methods, showing no significant difference between the two approaches (Fig. 79.2). Due to the heterogeneity in surgical approach, it is difficult to compare outcomes of each technique. Therefore, more comparative studies are needed to establish further evidence.

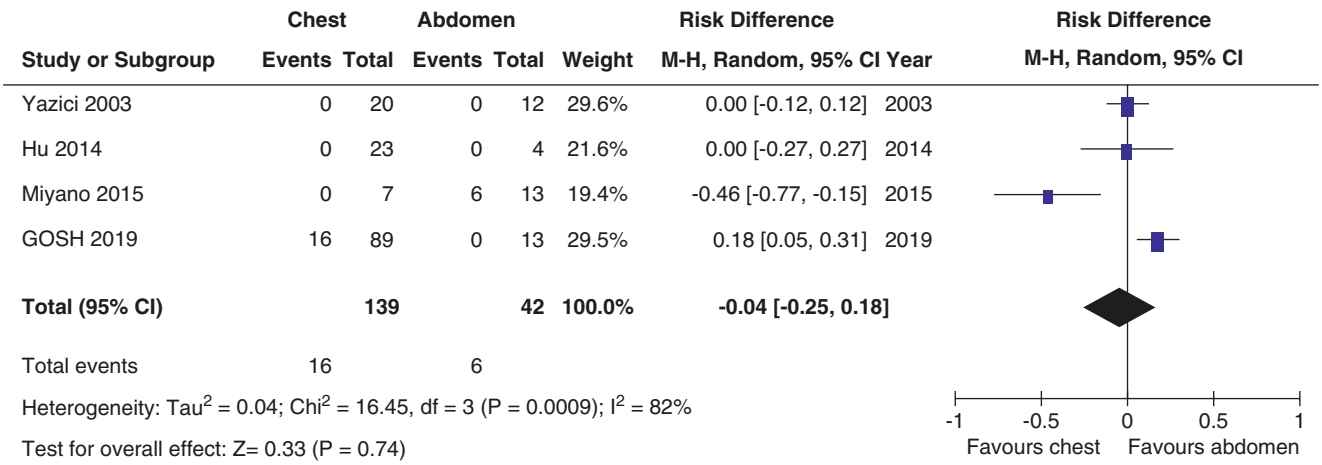

Fig. 79.2 Forest plot for recurrence comparing transthoracic and transabdominal approach. *GOSH* Great Ormond Street Hospital

Conclusion

Eventration of the diaphragm occurs in various situations and the manifestations and severity of the disease ranges according to the primary cause and degree of elevation. Symptomatic patients who do not show spontaneous resolution are candidates for surgical intervention. There are a variety of surgical approaches. The decision regarding surgical technique should be carefully made, considering the advantages and disadvantages of each technique and the patient's condition. Surgical outcomes are generally satisfactory, but it is important to make the diaphragm taut enough by ensuring effective sutures, as recurrence is likely to be technique-dependent.

Editor's Comments

Children with unilateral eventration of the diaphragm are often asymptomatic. Symptoms—tachypnea, recurrent respiratory infections, failure to thrive, inability to wean from mechanical ventilation—are an indication for surgical intervention. In cases where the eventration is related to traction on the phrenic nerve from birth trauma or chest surgery, spontaneous recovery can occur. Partial or complete resolution of the elevated diaphragm is usually seen within 3 months. Early surgical intervention should be considered in asymptomatic infants with severe eventration, as this can affect lung development. Although recurrence is uncommon, it is usually best to follow these patients with yearly chest radiographs for several years.

Congenital or acquired, the common etiology in the vast majority of cases is phrenic nerve injury or dysfunction with subsequent paralysis of the diaphragm. Plication does not address the underlying condition but prevents the eventual displacement and restriction of the lung by the paralyzed diaphragm as it stretches and billows upward. By flattening the diaphragm, the lung is allowed to expand and most people can breathe normally with a single normally functioning diaphragm. An injured or stretched but physically intact phrenic nerve can recover but axonal regrowth can take months. A patient whose phrenic nerve was severed or crushed traumatically or by a surgeon should be considered a candidate for nerve repair or sural nerve interposition grafting, a procedure increasingly available at specialized centers.

The thoracoscopic approach is straightforward and preferred by many, though some have suggested the recurrence rate is lower when plication is performed trans-abdominally. Excision of the redundant portion of the diaphragm is probably the best way to prevent a recurrence, especially in infants, but if breakdown of the suture line occurs, the result is a diaphragmatic hernia. Most surgeons use heavy non-absorbable interrupted sutures, placed in a way that distributes the tension evenly across the entire repair. This is critical but underappreciated—a repair in which 2–3 sutures are carrying most of the tension while the other 4–5 are in a floppy part of the diaphragm will likely break down. Extracorporeal knots (Roeder or square) seem to work well, but one must frequently check the status of the repair and have a low threshold to cut and replace any suture that is under too much tension. It is also probably best to use pledgets, as the sutures tend to cut through the diaphragm over time. The laparoscopic approach is especially useful when a fundoplication or gastrostomy tube is needed and can be done concomitantly. The principles of the actual repair are essentially the same as for the thoracoscopic approach, though an extra port is often needed for bowel or liver retraction.

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