Review Article

Management of Congenital Diaphragmatic Hernia: a Systematic Review

Abstract:

Congenital diaphragmatic hernia (CDH) is associated with high mortality due to lung hypoplasia, pulmonary hypertension and co-existent anomalies. This review highlights recent progress in the perinatal management of CDH and addresses long-term outcome issues for survivors indicating the need for multidisciplinary follow up.

Introduction

The first report of a Congenital diaphragmatic hernia (CDH) was made by Lazarus Riverius in 1679 as a necropsy of an adult [149]. The first report of a CDH in a newborn was made by George Macaulay in 1754, also as a necropsy finding, in an infant who died from respiratory failure a little over 1 hour after birth [150].

In 1761, Giovanni Battista Morgagni, wrote a review of diaphragmatic herniations with the first observation that CDH was associated with pulmonary hypoplasia [151]. In the review, Morgagni described the first case of a parasternal hernia in an older man, so it was named Morgagni hernia. In 1848, Vincent Alexander Bochdalek reported two cases in which he described the location of the diaphragmatic defect as being in the posterior-lateral aspect of the muscle, hence the origins of the terms Bochdalek hernia and Bochdalek foramen [152]. Although widely used, these terms are actually improper given that the mechanisms and exact location proposed by Bochdalek, namely "rupture of the lumbocostal triangle," proved later on to be inaccurate [153].

In 1940, the first survival of a neonate, who underwent CDH repair on the second day of life, was reported by Ladd and Gross [154].

In 1977, German and colleagues [155] reported the first child with CDH to survive after being placed on extracorporeal membrane oxygenation (ECMO). Since that time, it has become clear that ECMO plays a major role in maximizing the survival rates of neonates with CDH [101].

In 1992, Harrison presented a series of CDH treated by open prenatal repair of the diaphragmatic defect in humans, With survival rate of 28.6% of the operated fetuses [156].

In the early 1990s, from the work of Wung and coworkers, the concept of avoiding hyperventilation and minimizing barotrauma was introduced [102]. These principles have led to marked reduction in iatrogenic insult to the lungs, which was common in the old, aggressive ventilation strategies, and consequently significant improvement in survival [157].

In 1994, the Congenital Diaphragmatic Hernia Registry was created, as a meta-institutional organization dedicated to the exchange and analysis of data related to this disease, as well as to the design and implementation of multicentric prospective trials. This has had a major beneficial impact on CDH survival and management guidelines [158].

Epidemiology

The prevalence of CDH has been reported as being anywhere between 1 : 1,200 and 1 : 12,000 births [1-10]. Likely, the main reason for such disparities is the so-called hidden mortality of CDH, which relates to the fact that many babies die before making it to a referral center and thus are not included in the statistics. The better controlled studies show CDH as occurring in 1 : 2,107 to 1 : 3,163 births [1, 3-6, 8].

Results of a large study, by Torfs and colleagues [8] involving over 718,000 births and stillbirths in part of California, revealed that CDH occurred in 1 : 3,163 births and in 1 : 3,340 live births. Among the major congenital anomalies, CDH is one of the most common, accounting for approximately 8% of the cases [11].

There are no clear racial differences in the prevalence of CDH [6, 8]. The study by Torfs and colleagues showed a higher prevalence in rural rather than urban areas, but this has not yet been confirmed by other series. The prevalence of prematurity and weight deviations in neonates with CDH is not different from that of the general population. While isolated CDH is a little more common in boys than in girls (1.5 : 1), sex distribution is normal in CDH associated with other congenital anomalies and in the whole CDH population [8, 12].

The epidemiologic profile of familial cases of CDH differs little from that of the total of cases: it is slightly more common in males (approximately 2 : 1) [13, 16, 20]. The occurrence of familial CDH follows a pattern suggestive of multifactorial inheritance as the most likely mode of transmission, with recurrence estimated between 1.3% and 2% [8, 11, 15,

18]. The possibility that a genomic imprinting phenomenon takes place has also been proposed [19].

Embryology of the diaphragm

Development of the diaphragm:

The diaphragm comes from the mesoderm. Its development is complex and not yet fully understood. It results from the fusion of five embryonic components: [23] & proceeds as follows:

1. Septum transversum
2. The two pleuro-peritoneal membranes
3. Mesoderm of the chest wall
4. Mesentery of the oesophagus
5. The mesoderm around the aorta[24].

Anatomy of The Diaphragm:

The diaphragm is the dome shaped septum dividing the thoracic from the abdominal cavity. It is present only in mammals. It comprises two portions: a peripheral muscular part that arises from the margins of the inferior aperture of the thoracic cage (termed by anatomists as the 'thoracic outlet') and a centrally placed aponeurosis [25].

The muscular fibres are arranged in three parts:

1: A vertebral part, from the crura and from the arcuate ligaments. The right crus arises from the front of the bodies of the upper three lumbar vertebrae and intervertebral discs; the *left crus* is attached to only the first two vertebrae. The arcuate *ligaments* are a series of fibrous arches, the *medial* being a thickening of the fascia covering psoas major and the *lateral*

of the fascia overlying quadratus lumborum. The tendinous medial borders of the two crura join each other in front of the aorta to form the *median arcuate ligament*.

2: A costal part, is attached to the inner aspect of the lower six ribs and their costal cartilages.

3: A sternal portion consists of two small slips from the deep surface of the xiphisternum .

The central tendon, into which the muscular fibres are inserted, is trefoil in shape and is partially fused with the undersurface of the pericardium [25].

Vascular system of the diaphragm:

Arterial Supply:

The arterial supply to the superior surface of the diaphragm consists of two branches from the internal thoracic arteries—the pericardiophrenic and musculophrenic arteries—and two branches from the thoracic aorta—the superior phrenic arteries. All these branches are small. The major blood supply to the diaphragm is to the inferior surface. It comes from the inferior phrenic arteries, which arise from the aorta or the celiac axis just below the median arcuate ligament of the diaphragm. In a small percentage of individuals, the right inferior phrenic artery arises from the right renal artery. The inferior phrenic arteries also supply branches to the suprarenal glands [26].

Venous Drainage:

On the superior and inferior surfaces, the veins run with the arteries [27].

Lymphatic Drainage:

All the diaphragmatic lymph nodes lie on the superior surface of the diaphragm. These nodes can be divided into anterior, middle, and posterior groups. They receive drainage from the upper surface of the liver, the gastroesophageal junction, and the abdominal surface of the diaphragm. Efferent lymph vessels from these nodes drain upward to parasternal and mediastinal nodes anteriorly, and to posterior mediastinal and brachiocephalic nodes posteriorly [27].

Nerve Supply of The Diaphragm:

The right phrenic nerve enters the diaphragm through the central tendon just lateral to the opening for the inferior vena cava. Occasionally it passes through that opening with the vena cava. The left phrenic nerve pierces the superior surface of the muscular portion of the diaphragm just lateral to the left border of the heart [26].

The peripheral portions of the pleura and peritoneum have an independent sensory innervation that arises from the 7th to the 12th intercostal nerves [27].

The sensory nerve fibres from the central part of the diaphragm also run in the phrenic nerve; hence, irritation of the diaphragmatic pleura (in pleurisy) or of the peritoneum on the undersurface of the diaphragm by subphrenic collections of pus or blood produces referred pain in the orresponding dermatome, the shoulder tip [25].

The diaphragm receives its entire motor supply from the phrenic nerve (C3, C4, C5), whose long course from the neck follows the embryological migration of the muscle of the diaphragm from the cervical region . Injury or

operative transection of this nerve results in paralysis and permanent elevation of the ipsilateral half of the diaphragm [27].

Natural History of Congenital Diaphragmatic Hernia:

Etiology:

The etiology of CDH is unknown. In a few rare syndromes in which a diaphragmatic defect is present is there a well-defined genetic cause, such as in trisomies of the chromosomes 13 and 18. On the other hand, a single institution review showed that 17% of all cases of CDH (i.e., both isolated and in association with other congenital anomalies) had a recognizable genetic etiology [22].

In addition, there was no concordance for CDH among five monozygotic twin pairs. These findings, in conjunction with previous reports of de novo dominant mutations in CDH patients, suggest that new mutations may be an important mechanism in the etiology of this disease. At the same time, the discovery of CDH loci using standard methodology has been hindered by the genetic heterogeneity of this disease. Relatively novel techniques such as array comparative genomic hybridization, whole-transcriptome expression profiling, and whole-exome sequencing, among others, are now being pursued and already shedding new light upon the extent and relevance of specific genetic abnormalities associated with CDH [28-33].

Even so, the twin data also point to the possibility that epigenetic abnormalities contribute to its development. Indeed, experimental CDH can be produced in diverse animal species through a variety of interventions, other than surgical creation of the defect, including: exposure to diet

deficient in either vitamin A [34, 35], zinc [36], or cadmium[37]; administration of either thalidomide [38], anti-rat rabbit serum[39], 2,4-diclorophenil-p-nitrofenilic ether (nitrofen, an herbicide) [40-42], or polibromate biphenils [43, 44]; induction of endothelial heparan sulfate deficiency [45]; and genetic manipulations, such as FOG-2, COUP-TFII, GATA-4, SOX7, and Slit3 mutations [46-50] However, to date, there's been no conclusive relationship between these experimental models and clinical/epidemiological data in humans.

Pathophysiology:

The cardinal aspects of CDH pathophysiology are pulmonary hypertension with persistence of a fetal circulatory pattern, along with a reduction in both pulmonary tidal volume and compliance. The intensity of such manifestations varies a great deal, going from almost nonexistent to incompatible with life, depending mostly on the severity of the anatomical abnormalities of a given patient. According to some, a deficiency of the surfactant system is also part of CDH pathophysiology [51-54]. However, this notion has been increasingly challenged by more recent data [55-57]. In children, total peripheral airway cross section area is proportionally larger than in adults, hence the reduction in airway generation present in CDH usually does not lead to significant increases in airway resistance [58].

The difficulty in ventilating children with CDH stems mostly from the lower pulmonary compliance and lower tidal volumes. The pressure-volume curves of these hypoplastic lungs are abnormal, so that, at a given pressure, lung volume is lower than normal [59].

Microscopic analyses under insufflation show that, while certain air-spaces may open at 15-20 cm H2O, many are still closed at 30-35 cm H2O

[60]. Thus, higher inspiratory pressures are transferred only to the alveoli that are open, leading to alveolar rupture and a tendency to develop pneumothorax [61].

It is not yet clear whether the decreased pulmonary compliance is a result of a quantitative and/or qualitative depression of the surfactant system, or a relative increase in the total amount of collagen in the lungs [51-53, 62].

The lower tidal volumes are a direct consequence of the reductions in both lung volume and total alveolar number [63-66]. All these ventilatory abnormalities are the main reasons for the tendency of infants with CDH to retain CO2 [61].

Contrary to what happens with the airways, the peripheral vessels (lower arteries, arterioles, and capillaries) account for most of the pulmonary vascular resistance (PVR). Therefore, as a result of the reduction in the total number of arterial branches and their lower than normal diameters, the total arterial cross sectional area is diminished and the PVR is usually significantly increased in CDH [67, 68].

Further contributing factors to the increased PVR are the hypermuscularization of the arteries and amplified arterial reactivity. Because of the latter, certain physiological stimuli such as alveolar hypoxia, hypoxemia, hypercapnia, acidosis, cyanosis, hypothermia, as well as any "disturbances," such as certain inflammatory mediators and simple manipulations of the patient, may trigger intense pulmonary vasoconstriction and marked increase in PVR [69, 70].

Other than the role played by the muscular hypertrophy present in pulmonary arteries and arteriolae with increased PVR, the reason why these

vessels tend to overreact to stimuli is not yet known. Recent data suggest that the pulmonary vasculature's ability to synthesize nitric oxide is depressed in CDH and thus may be part of the mechanism [71].

The possibility of an imbalance involving prostanoids, which are vasoactive agents that include prostaglandins, playing a role has been suggested [68, 72-74]. A potential role for other endogenous vasoactive agents, such as endothelin, in the increase in PVR has proved debatable [68, 75, 76].

This increase in PVR leads to pulmonary hypertension, which is almost universally observed in neonates with CDH [60, 68, 77] Pulmonary hypertension leads to a decrease in total blood flow to the lungs, an increase in end-diastolic pressure in the right ventricle, and a tendency for persistence of a fetal circulatory pattern, with right-to-left shunt through the ductus arterious and foramen ovale [60, 69].

The decrease in total pulmonary blood flow and the right-to-left shunt lead to hypoxemia, hypercapnia, and acidosis, which in turn are stimuli to pulmonary vasoconstriction, which worsens the pulmonary hypertension, with consequent intensification of the fetal circulatory pattern and so forth, establishing a vicious circle difficult to break. Not infrequently, patients may be satisfactorily oxygenated and fairly stable, until a random stimulus, or nothing immediately discernible, triggers the vicious circle of fetal circulation. Such a period of temporary stability that precedes the emergence or worsening of pulmonary hypertension has been coined honeymoon. It was described for the first time by Collins and colleagues [68, 78] in the mid-1970s and remains a frequent observation in neonates with CDH.

The mechanisms responsible for the end of the honeymoon have been elusive until the last few years, when mounting evidence points to it being a

cardiac event, more specifically variable degrees of right heart failure [79]. Patients who present soon after birth with persistent hypoxemia, without ever going through a honeymoon period, usually have severe pulmonary hypoplasia and serious abnormalities of the pulmonary vasculature [80].

In the fetus, the oxygenated blood that comes from the placenta returns to the right heart through the umbilical vein and crosses either the foramen ovale or the ductus arteriosus toward the aorta, so that only approximately 7% of the cardiac output goes through the lungs [81].

Therefore, the hemodynamic disturbances associated to pulmonary hypertension almost never manifest in utero. After birth, however, the hemodynamic status tends to deteriorate, often with overload and potential failure of the right heart. Thus, cardiac failure is typically part of the pathophysiology of CDH [79, 82, 83] and survival depends, to a great extent, on the ability of the myocardium to withstand the overload imposed by the pulmonary vasculature [60, 79, 82].

The deviation of the mediastinum by the herniated content may lead to a decrease in the venous return to the heart, possibly contributing to further worsening of the patient's hemodynamic status.

It has been suggested that neonates with CDH may have adrenal insufficiency, with an inadequate response to stress [84]. At the same time, there is preliminary experimental evidence pointing to the possibility that lower than normal glucocorticoid levels can contribute to the abnormal lung development and maturation found in CDH [85].

The true meaning of these findings in CDH pathophysiology remains to be better defined. Indeed, at least as far as receptors are concerned,

hypoplastic lungs of fetuses and newborns with CDH seem to be as responsive to glucocorticoids, thyroid hormone, and retinoic acid (all relevant to normal pulmonary development) as the lungs of normal children [86].

Clinical manifestations:

Approximately 90% of the patients with CDH are symptomatic within the first 24 hours of life . Yet, this disease can first manifest at any age and, more rarely, go unnoticed until late in life, or even never be diagnosed [87, 88].

When a child is symptomatic within the first 24 hours of life, the main clinical manifestation is respiratory distress. The earlier the onset of signs and symptoms, the more severe the pulmonary hypoplasia. Newborns that are symptomatic in the first 6 hours after birth are considered high risk and account for 88% of the cases. Tachypnea associated with sternal, subcostal, and supraclavicular retraction is common. Cyanosis and pallor are also frequent. Apgar scores tend to be low [87].

If untreated, the dyspnea tends to worsen over time for three reasons: the progressive distention of the intrathoracic bowel by gas, which is accelerated by aerophagy, common in children in respiratory distress; the gradual increase of the volume herniated to the chest, which is a result of the negative pressure exerted during respiration; and the escalating hypoxemia, hypercapnia, and acidosis because of the vicious circle generated by persistent pulmonary hypertension. The abdomen is often scaphoid because of the migration of abdominal viscera to the chest [87].

However, because of possible bowel distention inside the abdominal cavity, the abdomen can assume a normal appearance over time. The chest

may be asymmetrical and larger on the side of the hernia, especially after the bowel fills with gas. The heart sounds are commonly dislocated to the contralateral side of the hernia or in the midchest. Sometimes, the same happens with the trachea. In the ipsilateral hemithorax, the respiratory sounds may be diminished or absent altogether, while bowel sounds may be present. There may be hemodynamic instability, with a tendency to arterial hypotension, because of a decreased venous return to the heart due to the mediastinal deviation and/or because of right heart failure due to pulmonary hypertension. Occasionally, mediastinal deviation can also lead to superior vena cava syndrome [89]. If it goes untreated, a symptomatic newborn usually dies within a few minutes or hours.

When CDH first manifests after the neonatal period, partial or complete gastrointestinal (GI) obstructions are more common than respiratory distress, which, if at all present, tends to be mild. Unlike in the neonates, the spectrum of manifestations of late presentation CDH is broad, including (in addition to GI obstruction and respiratory distress) sudden death, growth retardation, perforations or strangulations of intrathoracic hollow viscus (which can lead to sepsis, empyema, pneumothorax, or hemothorax), rupture of a herniated spleen (with hemothorax, anemia, and possibly hypovolemic shock), airway infections or recurrent pneumonias, urinary tract obstruction owing to herniation of the ureter, chest pain, abdominal pain, vomiting, diarrhea, anorexia, acute abdomen, intrathoracic appendicitis, and other rare presentations [87, 88, 90].

DIAGNOSIS:

The majority of cases are diagnosed before birth, during routine prenatal ultrasound [91]. The relative proportion of cases diagnosed in utero is

constantly climbing, because of the increasing application of prenatal ultrasound screening and improvements in ultrasound technology and resolution.

Fetal ultrasonography should always be performed whenever there is polyhydramnios, given that CDH is one of its causes, apparently because of a reduction in the volume of amniotic fluid swallowed by the fetus and probably because of the GI obstruction caused by the hernia. A few authors also recommend careful ultrasonographic examination whenever an amniocentesis shows abnormally low levels of lecithin and sphingomyelin in utero, because of the possibility of an association between CDH and a deficiency in the surfactant system [53, 54]. Such an association, however, has become less accepted [55-57, 92].

CDH can be diagnosed with prenatal ultrasound from the eleventh week of gestation until term; previously negative examination results can become positive at any time during pregnancy [91, 93].

False-negative and false-positive examination results can occur; fetal ultrasonography is precise in approximately 90% of cases [69, 94].

The herniated content identified by prenatal ultrasound can move in and out of the chest, as if the hernia were a dynamic process [95].

A case of CDH diagnosed in the second trimester of pregnancy that seemed to have resolved spontaneously during the third trimester, with delivery of a normal infant, has been reported [96].

The differential diagnosis of CDH identified by prenatal ultrasound includes congenital cystic adenomatoid malformation (CCAM) of the lung, diaphragmatic eventration, Morgagni hernia, hiatal hernia, pentalogy of

Cantrell, primary diaphragmatic agenesis, pericardial hernia, pulmonary sequestration, lung cysts, diaphragmatic duplication, leiomyosarcoma of the lung, mediastinal teratoma, esophageal atresia with tracheoesophageal fistula, primary pulmonary agenesis, primary pulmonary hypoplasia, and intrathoracic duplications of the GI tract [69, 97].

After birth, a plain chest radiograph is almost always enough to confirm the diagnosis. The typical image is that of bowel loops seen within the lung fields, with deviation of the mediastinum to the contralateral side of the hernia, and decrease or absence of gas in the abdomen. When the radiograph is obtained before the GI tract can be filled with gas, or if the intestines are not herniated (which is more common in right hernias), there may be confusion in the diagnosis.The introduction of a radiopaque gastric tube often helps, in case the stomach is herniated . Should any uncertainty persist, which is uncommon, the diagnosis can be confirmed with a radiograph performed after infusion of contrast through the gastric tube [98].

Even less frequently, an ultrasound may be of help. More rarely, CT, MRI, or a contrast enema can have a role. The differential diagnosis of CDH after birth includes diaphragmatic eventration, pneumonia, CCAM, lung cysts, pneumothorax, pleural collections, Morgagni hernia, hiatal hernia, primary agenesis of the diaphragm, primary pulmonary agenesis, primary pulmonary hypoplasia, pericardial hernia, pulmonary sequestration, cardiac tumors, and duplication of the diaphragm. Despite all these possibilities, the diagnosis of CDH after birth tends to be relatively easy [99].

On late presentation CDH, the diagnosis is usually made with a simple chest radiograph as well. Also in these cases, a gastric tube may be of help during the interpretation of the radiograph. Sometimes there is previous

history of a normal chest radiograph. One must always remember the possibility of late presentation CDH, otherwise the diagnosis will likely be delayed and confused with either pneumonia, pneumatoceles, CCAM, pneumothorax, pleural collections, diaphragmatic eventration, lung cysts, lung nodules, or pulmonary sequestrations. Given that late presentation CDH is relatively rare, the need for other examinations in addition to the chest radiograph is somewhat more common. Such examinations can include an upper GI (often with the patient in Trendelenburg position), ultrasound, CT, MRI, fluoroscopy, and, more rarely, a contrast enema. CDH may be diagnosed as an incidental imaging finding in an asymptomatic patient [100].

Defects are classified according to Congenital diaphragmatic hernia study group staging system (CDHSG) staging system as: A: smallest defect, usually "intramuscular" defect with >90% of the hemi-diaphragm present; this defect involves less than 10% of the circumference of the chest wall, B: approximately 50%–75% of the hemidiaphragm is present and less than 50% of the thoracic wall is involved in the defect, C: less than 50% of the diaphragm is present and greater than 50% of the thoracic wall is involved in the defect, and D: largest defect, minimal or no diaphragm is present – also known as "agenesis".

Treatment:

Surgery:

Timing of Operation:

With an improved understanding of its pathophysiology, repair of CDH is no longer considered an emergency procedure. However, the optimal

timing for repair remains unclear. Historically, early repair was thought to improve ventilation by reducing intrathoracic pressures after reduction of the herniated viscera. However, this strategy often led to urgent procedures being performed on unstable infants [101].

A paradigm shift in management to delay the operative repair until the infant is stable became widely adopted in the early 1990s [102, 103]. Several studies have shown no difference in mortality rate or the need for ECMO in infants undergoing early vs late repairs, including two randomized trials of early (<12 hours) versus delayed repair after 24 hours [104] and after 96 hours [105].

Today, repair of CDH is usually delayed until cardiopulmonary stability is achieved, although the definition of physiologic stability remains highly variable and inconsistent amongst centers [106].

In 1995, Wung et al. reported advantages with a delayed repair strategy for CDH [102] Comparing three eras of treatment strategies, the study contrasted an early period of emergency surgery to the most recent era of delayed repair and 'gentle ventilation,' where infants with CDH were managed with a lung-preserving ventilation strategy. Repair was not performed until the pre- and postductal *Sp*O2 gradient equalized and right-to-left shunting on echocardiogram had resolved. With an average of 4.2 days after birth before operation, survival was 94% with only one patient requiring ECMO. From the same institution in 2002, 120 consecutive patients were treated with permissive hypercapnia, spontaneous respiration, and elective repair after 36 hours of life with an overall survival of 84% [107]. Only 13.3% of patients needed ECMO and only 7% of infants required a prosthetic patch, suggesting a relatively small proportion of

infants with large diaphragmatic defects. A different group reported similar results from a center that did not offer ECMO [108].

In this study, all high-risk patients (defined as assisted ventilation within two hours of life) were divided in three historical cohorts with the most recent group being managed by permissive hypercapnia, gentle ventilation, and delayed repair until hemodynamic stability was achieved (*Pa*CO2 < 60 mmHg, *Pa*O2 > 40 mmHg, *Sa*O2 > 85% with a *Fi*O2 < 50%) for at least 48 consecutive hours. Overall survival in this recent cohort was 90%. Despite the benefits of preoperative stabilization and delayed repair, the specific parameters that define hemodynamic stability and timing of operation remain unanswered.

According to data from the Congenital Diaphragmatic Hernia Registry (CDHR) and Extracorporeal Life Support Organization (ELSO) over a recent 15 year period, one-third of infants with CDH required ECMO during their initial hospitalization, during which 85% of these infants underwent early CDH repair on ECMO [109].

Operative Approach:

Open repair of CDH can be performed using a thoracic or abdominal approach. Advantages to laparotomy include easier reduction of intrathoracic viscera, the 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 incision (91%) [110, 111].

Less than 10% are performed via a thoracotomy. The intra-abdominal contents should be reduced out of the thorax with careful attention to the

spleen that can be caught and lacerated on the rudimentary rim of diaphragm [112].

The thoracic and abdominal cavities should be inspected for an associated pulmonary sequestration. Despite this 'gold standard' abdominal approach, the morbidity and respiratory sequelae of open CDH repair remain a concern. In addition to pulmonary hypoplasia and hypertension, respiratory compliance is significantly reduced after open repair. Mortality significantly increases when compliance decreases by >50% which can occur as a result of a tight abdominal wall closure [113, 114].

Careful attention should be paid to the peak airway pressures as the abdominal fascia is closed. Respiratory compromise should alert the surgeon to leave the abdomen open. This approach is more often needed in CDH infants on ECMO [115]. Temporary closure can be achieved using just the skin or a prosthetic silo. Delayed closure, especially in those infants on ECMO, should be attempted after the generalized edema has resolved or the intra-abdominal domain has enlarged [116].

The routine use of chest tubes after CDH repair to drain pleural fluid has been abandoned [108, 117]. One concern is that the chest tube can cause ipsi- and contralateral lung injury secondary to mediastinal shift, especially if connected to suction. The thoracic space will eventually fill with fluid, and the lung will gradually grow. Tube thoracostomy should only be used for postoperative chylothorax or pleural fluid causing hemodynamic compromise [118]. If a chest tube is needed, it is positioned in the thoracic cavity prior to final closure of the diaphragm.

Chest tubes should be placed to water seal rather than suction. Symptomatic pleural fluid can be treated with repeated thoracentesis. If used, chest tubes should be removed early to avoid infectious complications.

Minimally Invasive Techniques:

The respiratory sequelae and other morbidity seen after open CDH repair has prompted surgeons to adopt minimally invasive surgical (MIS) approaches. Both thoracoscopic and laparoscopic repairs have been performed. Data from the CDHR show that laparoscopic and thoracoscopic strategies are being used worldwide, and have been utilized in 20% of centers since 1995 [119]. MIS techniques have been used for primary repair as well as prosthetic patch closure with suggested advantages of less postoperative pain, avoidance of thoracotomy-associated complications, and an overall reduction of surgical stress [120, 121].

The sensitivity of CDH infants to hypercapnia and acidosis has drawn concerns regarding the utilization of MIS. The overall benefits of MIS are questioned because: (1) CDH neonates may absorb the CO2 insufflation [122, 123]; and (2) insufflation with CO2 can raise intracavity pressures that may limit venous return, end-organ perfusion, and tidal volume. The combination of CDH-related pulmonary hypoplasia, PHTN, and labile pulmonary vascular reactivity may be detrimental during MIS operations. Although increases in CO2 absorption during MIS are generally well tolerated in infants, CDH neonates specifically demonstrate greater changes in end-tidal CO2 (ETCO2) and impaired elimination of CO2 during thoracoscopy and laparoscopy [124, 125].

Hypercapnia and the associated acidosis may result in increased pulmonary shunting. Patient selection is paramount for successful completion of an MIS repair as well as for minimizing operative morbidity [125].

Historically, MIS was reserved for stable infants with anticipated small defects. Utilizing anatomic markers such as stomach herniation, surgeons have attempted to predict which defects might be amenable to MIS repairs [126].

Initially, the radiographic presence of the nasogastric tube within the abdomen and minimal respiratory compromise (PIP < 24 mmHg) were thought to predict a successful thoracoscopic repair. One group reported 95% success rates with thoracoscopic repairs when patients did not have a significant congenital cardiac anomaly or the need for preoperative ECMO, and had a PIP ≤ 26 cmH2O, and an oxygenation index ≤5 on the day of surgery [127].

Large defects that require patch repairs [127, 128] and right-sided defects are no longer contraindications to MIS [129].

However, patients undergoing MIS repair of CDH should have strict intraoperative monitoring of ETCO2 and *Pa*CO2.226 Although success with laparoscopic [121, 130] and thoracoscopic [131, 132] repairs have been reported, comparative evidence between MIS and open approaches has been limited to single-institution experiences or retrospective analyses [132].

In another report, a systematic review and meta-analysis of neonatal endosurgical CDH repairs identified only three eligible studies comparing open to endosurgical repair [133]. The cumulative risk ratio for death was

0.33 in favor of the MIS approach and recurrence was 3.21 in favor of the open repair. The overall survival rate for MIS patients was significantly higher compared with patients undergoing open repair (82.9% open and 98.7% MIS, $P < 0.01$) [127].

These results suggest a significant survival advantage for the MIS approach. However, the data are more likely the result of selection bias based on surgeon preference regarding which patients were good candidates for MIS. Although the ability to perform MIS repair of CDH has been shown, the short- and long-term outcomes regarding the durability and recurrence rates for an MIS approach are less clear. The reported overall recurrence rates for MIS repair range from 5–23.1% [127, 128], with early recurrences as high as 23–33% [134].

In another study, MIS repairs were performed in only 3.4% infants with CDH, but had a significantly higher in-hospital recurrence rate compared to open (7.9% vs 2.7%, $P < 0.05$) [110].

The true risks and benefits of the MIS approach for CDH repair, including the impact of reoperations, remain unclear. At the very least, recurrence seems to be higher [135].

Robotic CDH repair has been demonstrated to be feasible and safe Proponents of robotic CDH repair tout the increased degrees of freedom of the articulating instruments for suturing [136].

Diaphragmatic Substitutes:

Repair of large diaphragmatic defects is a challenge, usually requiring diaphragmatic replacement with a prosthetic patch or autologous tissue. In

one large study, 48.3% of infants undergoing CDH repair required diaphragmatic replacement [110].

Comparative studies between patch and primary repairs have consistently shown increased morbidity and mortality in the patch groups, most likely due to the large defect size and the associated severity of the pulmonary hypoplasia [137, 138]. In many studies, patch repair has been utilized as a surrogate for defect size and disease severity (i.e., larger the defect = increased severity of disease).

Nonabsorbable Synthetic Patches:

Synthetic patches such as polytetrafluoroethylene (PTFE or Gore-Tex®) or composite polypropylene (Marlex®) represent the majority of the mesh replacements used in neonates with a large CDH [139]. Advantages to synthetic patches include: (1) immediate availability; (2) minimal preparation time; (3) easily cut to fit the diaphragmatic defect; and (4) less tissue dissection, reducing the risk of hemorrhage, especially during repair on ECMO [140].

However, there are several disadvantages to synthetic patches for CDH repair. PTFE, anchored to the chest wall, can potentially produce a tethering point for creating a pectus-type deformity[140]. There is an increased incidence of bowel obstruction, need for splenectomy, patch infections, and abdominal wall deformities when patches had been used in old reports [139, 141].

The overall recurrence rate has been reported to be as high as 50% with a bimodal distribution showing early recurrence in the first months after repair and late recurrence years later[139].

Early recurrences for defects requiring a patch are most likely due to lack of tissue adhesion or scarring and an incomplete muscular rim which then requires anchoring the patch to the ribs or esophagus. PTFE tends to scar and retract over time, which may lead to late recurrences in the growing child. In an effort to prevent CDH recurrence, one group described a coneshaped, double-fixed PTFE patch to allow expansion over time [142].

The recurrence rate decreased from 46% to 9% at one year after repair. Similar results have been seen with a mesh plug and patch technique in the setting of a recurrent CDH [143]. Another group described a doublesided composite patch consisting of PTFE and type-1 monofilament, macroporous Marlex. Utilizing a pledgeted, nonabsorbable running suture, the recurrence rate .

Postoperative Care:

If the patient was not on ECMO during surgery, mild ventilatory support under flow synchronization, should resume as soon as possible, if necessary with pharmacologic reversal of the muscle paralysis, in case it had to be used. This transition can be tremendously facilitated if the child was placed under continuous epidural anesthesia intraoperatively [144].

The principles guiding mechanical ventilation described for the preoperative period also apply to the postoperative period. The same is true for the criteria to go on ECMO [145].

Although some children improve after repair of the hernia, frequently there is (at least temporary) deterioration of the respiratory mechanics in the immediate postoperative period[146].

This phenomenon is thought to be due to anatomic distortions on the diaphragm and thoracic cavity, to hyperinflation of both lungs, and to an increase of the intra-abdominal pressure [146].

Under these circumstances, the ventilator parameters may need to be temporarily “increased,” sometimes to the point that alternative modes of ventilation and even ECMO may have to be used. Occasionally, children that had been on bypass preoperatively and were decannulated before the operation may need to go back on ECMO [146].

Another potential complicating factor is the administration of intravenous fluids, which must be controlled carefully. Concomitantly to the common risk of hypovolemia, related to surgical trauma and bleeding, neonates with CDH, more so than newborns with other surgical diseases, initially behave as if with inappropriate secretion of antidiuretic hormone and may tend to retain excessive amounts of water. The explanation for this phenomenon is not yet clear. This predisposition must be recognized early, otherwise patients can be overloaded with fluids, with harmful consequences to their respiratory and cardiac status [147].

Sometimes, intra-abdominal pressure rises significantly in the immediate postoperative period. One should be attentive to signs of inferior vena cava syndrome, which can lead to a decrease in the venous return to the heart, impairment of renal blood flow, or a reduction in tidal volume. Should there be any evidence of renal insufficiency or major worsening of the respiratory or cardiac status, one must consider muscle paralysis, which may lower the intra-abdominal pressure. In the more severe cases, it may be necessary to take the child back to the operating room for placement of an abdominal silo [102].

Whenever the chest tube is used, it is not continuously aspirated, but only placed under a passive water seal to avoid alveolar overinflation, which can occur on both lungs because of the large empty residual space within the ipsilateral pleural cavity [102].

The chest tube should be removed only after the patient is extubated, usually after liquid drainage ceases. Not infrequently, liquid drainage lasts for a long period of time, until the lung can occupy the whole pleural space. In these circumstances, one may consider removing the chest tube while it is still draining fluid and tolerate a temporary pleural collection [102].

GI obstruction resulting from adhesions, gastric volvulus, or midgut volvulus can occur even in the immediate postoperative period. Other rare complications are chylothorax and chylous ascites. In the few cases reported to date, the causes for these chylous collections have not been clearly determined. Their treatment should be based on parenteral nutrition, feedings with middle chain triglycerides and, if necessary, occasional needle drainages [148].

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