Clinical Commentary

Congenital Diaphragmatic Hernia

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Congenital diaphragmatic hernia (CDH) is an anomaly that occurs in 1 in approximately 3,000 live births (1). Eighty-five percent are left sided and the commonest form is the classic posterolateral or Bochdalek hernia. There is a reported incidence of 40–50% of other malformations in association with CDH (2), the most common of which are those involving the central nervous system. The most important, in terms of prognosis, are congenital heart anomalies. Outcome data on this association are limited and confined to case reports or case series (3–5). On the basis of the physiology, it is likely that hemodynamically significant lesions associated with ventricular outflow tract obstruction (hypoplastic left heart syndrome, tetralogy, coarctation) or those with high pulmonary blood flow (atrioventricular septal defect, large perimembranous ventricular septal defects) will have more impact on mortality compared with atrial and small ventricular septal defects. CDH is also associated with chromosomal abnormalities both in number (Turner's syndrome, trisomy 13 and 18) as well as specific chromosomal aberrations (Fryn's syndrome). A rare familial association has also been reported (6). The spectrum of severity covers a wide range from infants with severe pulmonary hypoplasia and hypoxemia refractory to conventional and innovative ventilation techniques to those with a much more benign course and minimal blood gas derangements.

Gross (7) first reported a series of successful repairs in 1946 with 100% survival, and for the next 40 years CDH was considered the quintessential neonatal surgical emergency. However, his was a highly selected population, most of whom presented outside the first 24 hours of life. We now realize that the anomaly is far more complex than abdominal contents compressing the lung, which requires an operation to repair the defect and allow the lung to expand. The degree of pulmonary hypoplasia and the severity of the pulmonary vascular abnormality are the important issues that determine survival. Evidence suggests that the lesion includes failure of both alveolar and pulmonary vascular development (8). Expertise therefore needs to be focused away from the surgical aspects of CDH and onto techniques of mechanical ventilation and manipulating pulmonary vascular reactivity in order to improve outcome.

PRENATAL DIAGNOSIS AND INTERVENTION

Improvements in prenatal ultrasound have resulted in approximately 50% of these infants being diagnosed early in pregnancy, usually between Week 16 and Week 24 of gestation. The typical findings are presence of the stomach in the left chest (left-sided hernia) with the mediastinum shifted to the contralateral side. Right-sided defects are more difficult to diagnose and the abnormality can be missed if the stomach is not in the thorax at the time of the ultrasound examination. The pick-up rate is increased by accurate orientation of the mediastinal structures, principally the identification of all four heart chambers. A prenatal diagnosis of CDH does not mandate a change in obstetric management or the necessity for caesarean section.

Studies from the 1980s reporting the impact of prenatal diagnosis on outcome in CDH suggested that the finding of the defect early in gestation (< 18 weeks) was associated with high mortality. This was based on either single-center case series with a small number of patients or data collected by questionnaire from different pediatric surgical centers (9, 10). Nevertheless, there seemed to be a rationale for prenatal repair, especially in light of the high postnatal mortality reported at that time. These attempts were complicated by the high incidence of fetal loss from premature labor or kinking of the umbilical vein when the herniated liver was reduced in left-sided defects (11). The approach was then changed to a temporary plugging or clipping of the trachea, on the basis of animal studies showing that obstruction of egress of fluid from the lung during fetal life results in marked compensatory growth of alveoli (12).

A more recent innovation has been prenatal intervention based on prediction of severity, using the fetal lung-to-head ratio (LHR) as measured by ultrasound. An LHR < 1.0 combined with ultrasound diagnosis of CDH before 25 weeks and liver herniation has been associated with a high risk of poor outcome in some centers and has been used as the basis for a clinical trial of tracheal occlusion, using a fetoscopic technique (13, 14). The results have been disappointing. Preliminary reports show 5 of 15 survivors from the Fetal Diagnosis and Treatment Center at the Children's Hospital of Philadelphia (14). Details of follow-up over 2–4 years show that all have neurological problems. The San Francisco group report a 50% survival with no details on long-term follow-up (13).

The rationale for any prenatal intervention, using the criteria of poor outcome associated with a diagnosis of CDH made by ultrasound early in gestation, is no longer tenable as many centers now report a high number of successful outcomes in this patient population (4, 15, 16). Data published by the CDH Study Group on more than 400 infants have not shown a relationship between prenatal diagnosis and outcome (17). The LHR predictor used in the most recent trials has not been independently validated by other centers, apart from those doing active prenatal intervention. Any intervention must now be measured against the significant improvements in survival, now reported at more than 80% with reduced use of extracorporeal membrane oxygenation (ECMO), from large centers where the focus has been on innovative techniques of mechanical ventilation (18–20). Furthermore, a prenatal intervention is a risk to both mother and fetus that needs to be justified on the basis of clearly demonstrable improvements in survival or long-term morbidity. Prenatal counseling, including a decision on whether or not to continue

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TABLE 1. OUTLINE OF PRINCIPLES OF MANAGEMENT

- Resuscitation
  - ET tube placement with minimal bag mask/ventilation
  - Vascular access
  - Gut decompression by nasogastric tube
  - Ventilation objectives: preductal $Sa_{O_2} > 85\%$ and pH > 7.3 with PIP $\leq$ 25 cm H_2O
- Cardiopulmonary management
  - Ventilation
  - Conventional ventilation
  - Objective: preductal $Sa_{O_2} > 85\%$ pH > 7.3
  - PIP $\leq$ 25 cm H_2O
- HFOV
  - Objective: preductal $Sa_{O_2} > 85\%$
  - MAP $\leq$ 16 cm H_2O
- Pulmonary vascular management
  - Cardiac echo
    - Exclude CHD
    - Assess RV function
    - Estimate PA pressure
    - Identify the ductus and assess shunting
- Trial of inhaled nitric oxide for patients with increased RV pressure

Definition of abbreviations: CHD = congenital diaphragmatic hernia; ET = endotracheal tube; HFOV = high frequency oscillatory ventilation; MAP = mean airway pressure; PA = pulmonary artery; PIP = peak inspiratory pressure; RV = right ventricular; Sa_{O_2} = arterial oxygen saturation.

with the pregnancy, should not be based only on diagnosis early in gestation but rather on the presence of other anomalies and center-specific outcome data. The principal value in prenatal diagnosis lies in anticipatory management in a high-risk perinatal unit allowing for the early institution of therapies such as high-frequency oscillatory ventilation (HFOV) and the avoidance of potentially injurious forms of ventilation.

POSTNATAL RESUSCITATION AND STABILIZATION

The key principles of successful delivery room resuscitation and stabilization are based on the avoidance of high airway pressures and the establishment of a satisfactory (> 85%) preductal arterial saturation (Sa_{O_2}) (Table 1). An experimental study in a preterm lamb model of lung disease of prematurity has shown that as few as six high-volume lung inflations at the time of delivery results in pulmonary barotrauma and a blunted response to surfactant (21). Bag mask ventilation should be avoided to prevent gut distention. The objective of positive-pressure ventilation should be not to exceed 25 cm H_2O peak inspiratory pressure (PIP) and to target a preductal Sa_{O_2} of more than 85% while tolerating hypercarbia (Pa_{CO_2}, 45–55 mm Hg) if necessary as long as there is a compensated pH (> 7.35). Correction, using bicarbonate, if the pH is below that level is appropriate. The rationale for this approach is discussed in greater detail in the next section. Standard additional procedures should include insertion of a nasogastric tube as well as arterial and central venous lines. A preductal (right radial) Pa_{O_2} is preferred as this reflects the cerebral oxygenation. Although neuromuscular blocking drugs are frequently used during the initial resuscitation, their continued or routine use is not recommended, as there are no data suggesting that this improves outcome. Surfactant replacement therapy has also been advocated for infants who present with severe hypoxemia and low Apgar scores, on the basis of some encouraging results in animal models of CDH, but this is not supported by any human data. Principles for the safe transport of these infants include a secure airway, gut decompression, adequate vascular access, a compensated pH, and a preductal saturation of greater than 85%.

POSTNATAL PREDICTORS OF OUTCOME

There have been many attempts to assess the severity of CDH in the postnatal period as a basis for the need for alternative therapies, including ECMO. These have included X-ray assessment of contralateral lung size and the degree of blood gas derangement, particularly in relationship to the ventilation settings. In the past we assessed severity by a ventilation index, which was a combination of the Pa_{CO_2} with the peak airway pressure (8). This was based on the premise that lowering the Pa_{CO_2} by hyperventilation was important in preventing ductal shunting and improving survival. Because we have abandoned this approach and adopted a pressure-limited ventilation strategy this ventilation index is obsolete and we no longer use it. Other centers use the Pa_{O_2} and suggest that failure to demonstrate a preductal Pa_{O_2} of greater than 100 mm Hg at some stage of the resuscitation is incompatible with survival, even with the use of ECMO (22). In reality, the best validated postnatal predictor may turn out to be much simpler. A publication from the Congenital Diaphragmatic Hernia Study Group analyzed data submitted on 1,054 infants from 71 centers. The most significant predictors of outcome were the 5-minute Apgar score and the birth weight (5).

CARDIOPULMONARY MANAGEMENT

Mechanical Ventilation

The approach of deferred surgical repair in CDH has focused attention on ventilation techniques to improve oxygenation and, more importantly, on avoiding injury to the hypoplastic lung from positive pressure. A postmortem CDH study from our institution has shown that the previously high mortality in CDH can be partially attributed to pulmonary barotrauma causing damage to hypoplastic lungs (23). The management of persistent pulmonary hypertension of the newborn (PPHN) up to the past 5 years has included the use of hyperventilation to induce alkalosis, based on a small case series published in the early 1980s that demonstrated that this could reverse or eliminate ductal shunting (24). This has never been shown to improve outcome; rather, there is accumulating evidence that it may indeed be harmful in terms of pulmonary barotrauma and cerebral vasoconstriction. A "permissive hypercapnia" strategy was advocated by Wung and coworkers (25) in ventilation of infants with PPHN more than 15 years ago, well before it was introduced into adult medicine. Several case series of CDH have shown airway pressure limitation and tolerance of hypercarbia, while focusing on preductal oxygen saturation, to be the most important factors favorably influencing outcome (18, 19). The principal objective of mechanical ventilation should be to keep the PIP at 25 cm H_2O or less while maintaining a preductal Sa_{O_2} of greater than 85%. Ductal shunting can be tolerated as long as right heart function is adequate. This is based on lessons learned from newborn infants with cyanotic congenital heart disease: a normal lactate level, a mixed venous oxygen saturation (Sv_{O_2}) of greater than 70%, and the absence of metabolic acidosis are compatible with a good outcome.

Several centers are now opting to use HFOV as a way of avoiding barotrauma and report improved survival with deferred surgery (26–29). This had not been our experience when we routinely used hyperventilation between 1981 and 1995 (15), with HFOV as a rescue mode. We believe that our error was to use HFOV with a ventilation strategy that incorporated lung recruitment. However, unlike the other neonatal pulmonary diseases, CDH does not represent a recruitable lung and attempts to use a high mean airway pressure are likely to cause pulmonary damage. More recent case series have recommended mean air-

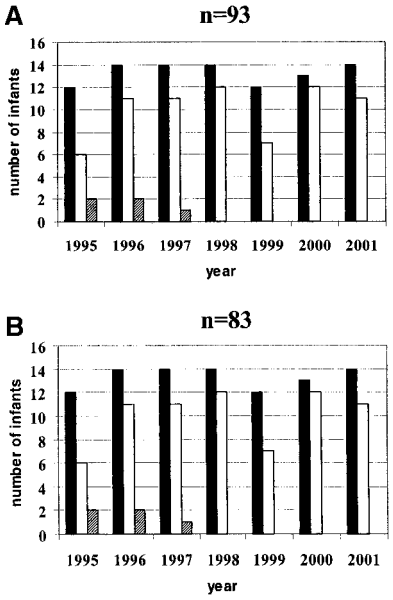

Figure 1. The outcome for 93 consecutive infants with CDH presenting in the first 12 hours of life, admitted to The Hospital for Sick Children between the years 1995 and 2001. (*A*) Outcome for all infants; (*B*) outcome excluding other major anomalies such as extreme prematurity, trisomy 18, and hemodynamically significant congenital heart defects. *Black bars* = total; *white bars* = survivors; *hatched bars* = ECMO.

way pressures no higher than 14–16 cm H_2O (27, 28, 30, 31). We have now changed our philosophy about the use of HFOV from a rescue mode to an early intervention strategy to limit lung injury when the PIP exceeds 25 cm H_2O on conventional ventilation. The peak-to-peak pressures (amplitude) are adjusted to achieve a Pa_{CO_2} in the range of 40–55 mm Hg. This generally requires a peak-to-peak airway pressure of 35–45 cm H_2O. The adoption of this strategy has been associated with a significant improvement in survival in our center since 1995 (Figure 1).

Pulmonary Vascular Management

Increased pulmonary vascular resistance is an almost universal finding in CDH even when not clinically manifest by right-to-left shunting at the ductal level. The diagnosis of PPHN in CDH is usually made on the basis of a pre/postductal saturation gradient. However, this occurs only when right ventricular pressure exceeds left ventricular pressure and, in the absence of this finding, there is little information about the level of pulmonary artery pressure. Therefore the information obtained by echocardiography is becoming increasingly important in the management of CDH, first to exclude an associated congenital heart defect but also to assess the degree of pulmonary hypertension. The cardinal echo features of increased pulmonary artery pressure are flattening of the intraventricular septum, development of tricuspid regurgitation, and right-to-left or bidirectional shunting at the ductal level. The presence of a tricuspid regurgitation jet allows the operator to actually estimate right ventricular pressure. Identification of the ductus is also important because as long as this is widely patent it allows the right ventricle to decompress and prevents right heart failure when the pressure becomes suprasystemic. A new finding of preductal desaturation, in a previously stable infant, might indicate that the ductus has closed or become restrictive and, if confirmed by echo, would warrant a trial of prostaglandin (PGE_1) to open the ductus and prevent right ventricular failure.

Although undesirable, ductal shunting is not harmful to the infant as long as preductal saturations are maintained at over 85%, as this reflects adequate cerebral oxygenation. The use of hyperventilation to reverse this is likely to do more harm than good in that it exchanges ventilator-induced lung injury for better systemic oxygenation. Infants who demonstrate significant ductal shunting or elevated right ventricular pressures can be tried on inhaled nitric oxide (iNO), although evidence for beneficial outcome of this therapy in CDH is lacking. Randomized trials of the use of iNO in PPHN have included infants with CDH, and they were the group that responded least well, with no impact on survival or the use of ECMO (32). However, it is more appropriate to monitor the response to iNO by echocardiography and, if a reduction of right ventricular pressure is documented, the therapy is worth continuing, accepting that it is unlikely that the dramatic reductions in pulmonary vascular resistance, seen in other forms of PPHN, will occur. Ductal shunting and low systemic pressures can also be improved by the use of volume loading with intravenous fluid and inotropic support, particularly if there is right heart dysfunction. However, there is no evidence to support the common neonatal practice of the routine use of high-dose dopamine and dobutamine in infants with PPHN.

Extracorporeal Membrane Oxygenation

There is now extensive experience with the use of ECMO in the management of CDH, originally in the rescue of infants with severe hypoxemia after surgical repair. Many centers now opt to use ECMO to stabilize an infant before repair and to perform the surgery either just before weaning or after decannulation. ECMO runs are frequently prolonged and venous cannulation prerepair may be problematic because of caval distortion when the liver is herniated. The overall survival of infants with CDH reported to the Extracorporeal Life Support Organization Registry is approximately 60%, which is the lowest in the various categories of neonatal acute hypoxic respiratory failure. Despite the better outcomes demonstrated in the UK randomized ECMO trial, the survival of CDH infants was poor ($< 20\%$) (33). Some centers with a previously high mortality ($> 70\%$) have seen an improvement in survival since the introduction of delayed repair and the use of ECMO (26, 34, 35). However, this must be placed in the context of centers now reporting equally good survival without the use of ECMO (36, 37). In a retrospective review of more than 400 infants with CDH from the Children's Hospital (Boston, MA) and The Hospital for Sick Children (Toronto, ON, Canada), outcome was compared between 1981 and 1994 (15, 16). In the Boston series ECMO was the predominantly used rescue mode, whereas in Toronto we used HFOV. The survival outcomes in the two institutions were the same (53 versus 55%). Fifty percent of the infants in the Boston series received ECMO compared with only 1% in our institution.

Apart from survival, published outcome studies of ECMO in CDH rarely address morbidity. The issue of neurological morbidity is particularly important and is higher in the CDH infants than in infants with other forms of PPHN (38, 39). In addition, a significant number of infants with underlying pulmonary hypoplasia have failed to separate from ECMO or survived with chronic lung disease, and for this reason some centers do not use ECMO in infants who have not demonstrated a preductal Pa_{O_2} of greater than 100 mm Hg or an Sa_{O_2} of greater than 90% at some stage of their resuscitation or stabilization (19, 20). A Cochrane review of published studies of the use of ECMO in CDH concluded that there is evidence for short-term efficacy, but it is unclear whether there is long-term benefit as defined as improved survival without major morbidity (40). Therefore, we would consider the use of ECMO only in those infants who decompensate with severe preductal hypoxemia and right-to-left shunting due to high pulmonary vascular resistance, for whom we are unable to maintain a preductal Sa_{O_2} above 85% and who fail to respond to iNO, inotropic support, or opening the ductus with PGE_1. We would not offer ECMO to infants with severe pulmonary hypoplasia, as defined by severe hypercarbia and the

inability to demonstrate a preductal Sa_{O_2} of more than 85% at some stage after initial resuscitation. Since 1995 we have used ECMO in only 6% of infants, and despite this the overall survival is over 75% among infants with CDH admitted to our institution, without any change in numbers treated in the past 20 years (Figure 1).

Surgical Repair

Studies published in the 1980s from this center showed that repair of the defect did not result in an improvement in gas exchange. On the contrary, thoracic compliance and Pa_{CO_2} actually deteriorated (41). These findings provided the rationale for delayed surgery and preoperative stabilization, which have now become generally accepted practice (42). The decision about timing of repair is based on evaluating the infant's hemodynamic and pulmonary profile. Surgery should be delayed until such time as there has been a reduction in pulmonary vascular resistance and satisfactory ventilation can be maintained with low PIP and inspired oxygen requirements. Infants with a low PIP and minimal shunting can be repaired within the first 24 to 48 hours of life, whereas infants who are labile with right-to-left shunting should have surgery deferred on a day-to-day basis until such time as they stabilize, even if this requires protracted periods of preoperative ventilation. When HFOV is used, we delay surgery until such time as the infant can be switched back to conventional ventilation and managed with peak airway pressures of less than 25 cm H_2O, as this meets our definition of stability. We do not undertake surgical repair in infants with preductal hypoxemia and hypercarbia, which cannot be reversed by therapies outlined in the previous sections. We believe that there is no potential for good outcome in these infants, even with the use of ECMO.

A detailed description of the actual technique for surgical repair is beyond the scope of this review. Gortex patches are commonly used for large defects that cannot be closed by primary repair without major distortion of the thorax. Reduction of the hernia with replacement of the abdominal viscera is frequently associated with difficult abdominal wound closure and an adverse change in respiratory system compliance (41). There is no indication to insert pleural drains at the time of surgery and they are needed only in the postoperative period in the event that there is an accumulation of pleural fluid that results in mediastinal shift or a contralateral pneumothorax (19).

OUTCOME AND FOLLOW-UP

The outcome for newborn infants presenting within the first 24 hours of life has changed significantly in the past 5 years. There have been several substantial case series from individual centers reporting a $> 75\%$ survival with decreased use of ECMO (18–20). The most recent outcome data from Columbia University (New York, NY) shows a 75% survival among their last 120 infants, with only 13% requiring ECMO support (20). This improvement they ascribe to the use of permissive hypercapnia, spontaneous respiration, and elective surgical repair. What these series have in common is that the focus has been on mechanical ventilation and the importance of limiting airway pressure and avoiding hyperventilation. We have seen survival in our own center increase from 53% in the period 1981–1994 to 75% among 93 consecutive infants between 1995–2001, using a strategy of pressure-limited ventilation, the early use of HFOV, and focus on the preductal Sa_{O_2} as the most important variable (Figure 1). If patients with major additional congenital anomalies are excluded, the survival rate increases to 84% (Figure 1).

Better outcomes in CDH mean that among the surviving infants are more marginal infants who previously would have died. This results in increased morbidity, with a rise in the number of reports of survivors with chronic lung disease, recurrent or residual pulmonary hypertension, gastroesophageal reflux, oral feeding aversion, poor weight gain, hernia recurrence, hearing loss, and delayed neurodevelopment (43–46). The extended hospital length of stay that is frequently involved has a major economic impact, estimated in one published series to be $98,000 per survivor if ECMO is not used and $365,000 with ECMO (47). These infants require more than the traditional surgical follow-up clinic visits and many centers, including our own, have now developed multidisciplinary clinics involving general surgeons, chest physicians, dietitians, neonatal follow-up specialists, and cardiologists. It is only with this co-ordinated approach that these medically challenging infants will receive the appropriate care for their ongoing problems.

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