Making the most out of the least: new insights into congenital diaphragmatic hernia

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Congenital diaphragmatic hernia (CDH) has an incidence of between 1:2000 and 1:5000 live births.[1] A posterolateral diaphragmatic defect allows abdominal viscera to herniate into the thoracic cavity early in gestation, inhibiting normal fetal lung growth and development.[2 3] Other pathophysiological features such as pulmonary hypertension, surfactant deficiency, and left ventricular hypoplasia may act synergistically to produce a mortality exceeding 60% even in the era of extracorporeal membrane oxygenation.[1 4] New insights into the pathophysiology of CDH will be reviewed and new treatment strategies emphasised.

Pulmonary hypoplasia, pulmonary hypertension and surfactant deficiency

A considerable reduction in the number of bronchial divisions occurs during development which is more severe on the ipsilateral side.[5] Bronchial divisions are arrested at 10–12 weeks on the side of the hernia and at 12–14 weeks on the contralateral side. This causes an overall reduction in the gas exchange area. In addition, the lungs appear to be arrested in the saccular phase of development. It has been argued that many infants dying of CDH have "lethal pulmonary hypoplasia".[6] However, this doesn't explain the "honeymoon period" during which they have adequate oxygenation and ventilation, but then deteriorate regardless of treatment.[6] Recently adopted "alveolar recruitment strategies" may help to explain this dichotomy.[7–9]

The lungs of patients with CDH have been found to have a decrease in size of the vascular bed,[10] abnormal muscularisation of the acinar arteries,[10] and an increased sensitivity to stimuli of pulmonary vasoconstriction.[11] The pulmonary vasculature cannot accept all of the right ventricular output at birth, resulting in the shunting of blood across the ductus arteriosus and foramen ovale. Although there has been an intensive search for mediators that cause pulmonary vasoconstriction in CDH, no single culprit has been identified. Endothelin-1, a potent vasoactive peptide, is increased during episodes of pulmonary hypertension, but the complicated actions of this protein make it difficult to determine whether it causes pulmonary vasoconstriction or is produced in response to it.[12 13] Increased thromboxane levels have also been found with episodes of pulmonary hypertension, but again results are confusing and the clinical significance unknown.[14–16] In addition, there is no evidence to suggest that there is a deficiency of nitric oxide (NO) production in CDH. Pulmonary nitric oxide synthase production has been shown to be identical in both surgically created CDH and control fetal lambs at term.[17] Nitric oxide synthase (NOS) activity was found to remain at control levels following ventilation, suggesting that a deficiency of NO production does not contribute to the pathophysiology of pulmonary hypertension in the surgically created lamb model of CDH.[17] Interestingly, decreased pulmonary NOS activity has been shown to be a pathophysiological feature in the nitrofen induced rat model of CDH.[18] Therefore, although an imbalance between vasodilators and vasoconstrictors has been hypothesised to explain the pathophysiology of pulmonary hypertension in CDH, others have maintained that pulmonary hypertension is an avoidable iatrogenic complication caused by aggressive ventilation and chest drainage.[19] It is believed that increased transpulmonary pressure causes perivascular emphysema and pulmonary hypertension (the "air block syndrome") with surfactant deficiency being the reason.

Histological, morphological, and biochemical similarities have been noted between the lungs of babies with respiratory distress syndrome and those with CDH.[20] Infants diagnosed prenatally with CDH have immature lecithin sphingomyelin (L/S) ratios and reduced levels of phosphatidyl glycerol (PG) in the amniotic fluid.[21 22] The fetal lamb model of CDH has been shown to have a quantitative and qualitative reduction in lung surfactant[23] with reduced total lung capacity and decreased compliance. A significant increase in lung compliance, total lung capacity, and oxygenation have been found in fetal CDH lambs treated prophylactically with surfactant (Infasurf; ONY Inc, Buffalo, New York, USA)[24 25] with a dramatic fall in pulmonary vascular resistance and subsequent increase in pulmonary blood flow.[26] This indicates that a portion of the pulmonary hypertension in CDH is due to alveolar instability and inadequate recruitment of all alveoli in a non-compliant lung.

Selection criteria for antenatal therapy

Timely fetal surgical correction of the diaphragmatic hernia has been shown to reverse both the pulmonary hypoplasia and the pulmonary vascular abnormalities in CDH.[27] Selection criteria for in utero surgical correction of CDH remains ill defined.[28 29] It is still impossible to determine prospectively which fetuses with CDH will survive the gestational or neonatal period, as only these groups should be candidates for repair of the diaphragmatic hernia in utero. The major challenge has been to identify prenatal risk factors in the fetus that will accurately select potential candidates for fetal surgery. Antenatal diagnosis before 25 weeks gestation has been used as the sole indication for fetal surgery, based on the finding that prenatally diagnosed CDH is associated with a mortality of 88%.[30] Others have shown that fetal age at diagnosis, polyhydramnios, dilated stomach in the chest, and mediastinal shift are limited in their prognostic usefulness and do not assess "fetal lung function" or neonatal outcome.[25 27 31] However, the "hidden mortality" in CDH is not entirely due to aberrant lung development.[29 32] Human necropsy studies and studies in the fetal lamb model have demonstrated left ventricular "smallness" in CDH.[33 34] Prenatal echocardiography has shown that ventricular disproportion (decreased left ventricular to right ventricular internal diameter ratios) noted before 24 weeks gestation is associated with a 100% mortality.[35 36] It has been speculated that such structural data generated echocardiographically as early as the pseudoglandular stage of lung development may be helpful in identifying fetuses with CDH that have lethal pulmonary hypoplasia.[37] Consequently, it has been suggested that the heart may be the "missing link" in the treatment algorithm

used to determine which fetuses should be considered for fetal surgery and which should be managed with state of the art postnatal care.[29 32]

Tracheal ligation, also referred to as "PLUG" (Plug the Lung Until it Grows), has been shown to reverse the pulmonary hypoplasia by accelerating fetal alveolar growth, and to reverse the pulmonary vascular abnormalities in CDH.[38 39] However, significantly decreased total phospholipid content by bronchoalveolar lavage and decreased surfactant synthesis by the type II pneumocytes in CDH have been described following tracheal ligation.[40] The clinical significance of these findings remains unknown as most animal data have been limited to short periods of study.[40] Long term studies are necessary to determine the clinical significance of these biochemical findings.

Postnatal therapy

If conventional mechanical ventilation does not stabilise the neonate with CDH, then alternative methods of oxygenation and ventilation should be considered. The primary abnormality of neonates with CDH who develop or maintain severe respiratory distress results from persistence of the fetal circulation – increased pulmonary artery pressures, increased pulmonary vascular resistance, and right-to-left shunting at the foramen ovale and the ductus arteriosus. This results in a vicious cycle of hypercarbia, acidosis, and progressive hypoxaemia. Surfactant therapy has been advocated even when the L/S ratio is normal, as bronchoalveolar lavage data have shown a qualitative and quantitative deficiency in surfactant phospholipids.[41 42] Infasurf (ONY Inc, Buffalo, New York, USA) should be administered intratracheally in a dose of 100 mg/kg before the first delivered breath.[23–25 43 44] Infasurf is a calf lung surfactant extract which includes surfactant associated proteins B and C. It has theoretical efficacy over the most commonly used artificial surfactant preparations Exosurf (Burroughs Wellcome, Research Triangle Park, North Carolina, USA) and Survanta (Beractant, Ross Laboratories, Columbus, Ohio, USA).[45]

Inhaled NO has been shown to improve oxygenation and survival in a lamb model of persistent pulmonary hypertension (PPHN).[46] Several case reports now indicate that inhaled NO may improve oxygenation in neonates with CDH.[7 47 48] Short term NO inhalation in CDH has been shown to improve oxygenation in neonates with CDH only after decannulation from extracorporeal membrane oxygenation (ECMO). It is speculated that this is related to maturation of the endogenous surfactant system during ECMO.[8] In contrast to infants with CDH, those with PPHN respond dramatically to inhaled NO.[7 46] This disparity in response to inhaled NO lies in the unique pathophysiology of CDH.[8 9] It appears that exogenous surfactant is required in the lamb model of CDH for delivery of inhaled NO to the terminal lung units, where it works synergistically with exogenous surfactant to decrease intrapulmonary shunting and PAP.[9] Similar efficacy has been achieved with combination inhaled NO and high frequency oscillating ventilation (HFOV) or perfluorocarbon associated gas exchange (PAGE), probably for the same reason.[46 49 50] All these strategies emphasise alveolar recruitment of the atelectatic, surfactant deficient lungs in CDH. Unless this strategy is utilised, NO may not be delivered to the alveolar capillary interface where it stimulates smooth muscle cell relaxation.

Neonatal resuscitation

An echocardiogram should be performed early to determine if any structural abnormalities exist, to assess for the presence of pulmonary hypertension, and to measure left ventricular mass index and left-to-right shunt fraction, to be repeated as frequently as necessary to reassess pulmonary haemodynamics and identify the direction of ductal level shunting, if any. If pulmonary hypertension with right-to-left shunting, left ventricular dysfunction, or systemic hypotension exist, vigorous use of inotropic agents is suggested to improve left ventricular function, increase systemic blood pressure, and reverse the right-to-left shunt. Efforts should be made to prevent factors that have been shown to increase pulmonary vascular resistance – for example, hypoxia, hypercarbia, acidosis, and hypothermia. We recommend gentle mechanical ventilation during this period in order to maintain a postductal saturation above 90%. The peak inspiratory pressure (PIP) should never exceed the steep portion of the pressure-volume (PV) curve generated by online pulmonary function machines (PEDS; MAS Inc, Philadelphia, Pennsylvania, USA). For each patient treated, individual PV data should be generated repeatedly to optimise ventilatory settings and to help avoid barotrauma to the hypoplastic and surfactant deficient lungs. Although more controversial, P_{CO_2} should be maintained at or below 8 kPa. No effort should be made to normalise P_{CO_2} at the expense of significant barotrauma, which may further compromise the quantitative surfactant deficiency with proteinaceous and/or bloody exudate.[24] Some centres have advocated "permissive hypercapnia" which tolerates moderately high P_{CO_2} levels as long as a post-ductal arterial P_{O_2} is maintained above 90%.[51] This strategy avoids overt barotrauma of the lungs.[51 52] In a small, non-randomised series Wung *et al* reported survival of 94% using this technique, avoiding ECMO in 95% of their patients.[51] Kays *et al* have successfully used a similar strategy with a survival rate exceeding 94% compared with 47% using standard therapy in combination with ECMO.[52]

Although less efficacious, neonates transferred to a tertiary care centre after a variable period of failed conventional mechanical ventilation should be considered for rescue with exogenous surfactant. Again, we recommend 100 mg/kg of a calf lung surfactant preparation given in a single dose with repeated doses if necessary. Need for continued gentle mechanical ventilation, support for inhaled nitric oxide therapy, HFOV, or ECMO therapy should be considered once these neonates arrive at tertiary care centres as they invariably have suffered significant barotrauma.

TIMING OF SURGERY AND ECMO

It has been shown that a delayed surgical approach, enabling preoperative stabilisation of these critically ill neonates, decreases morbidity and mortality.[53–56] Several reports now indicate that circulatory stability, respiratory mechanics, and gaseous exchange deteriorate after repair of CDH.[53 55 56] It is therefore better to stabilise the patient before attempting surgical repair. Although the ideal time to repair the diaphragmatic hernia is unknown, it has been suggested that 24 hours after stabilisation is ideal but, in fact, delays of up to 7–10 days are tolerated well.[57–59] It is probably prudent to operate on these neonates when echocardiographic evidence for normal pulmonary artery pressures is maintained for at least 24–48 hours.[60]

ECMO has become the final instrument to salvage the neonate with CDH who is refractory to conventional medical management.[61 62] Although initial reports did not indicate improved survival with ECMO, more recent series have reported survival of 80–90%.[62] The timing of operation also remains a major issue as it relates to ECMO therapy. The potential advantages of operating while on ECMO is based on the observation that postoperative

decline in pulmonary function can be controlled and recurrent pulmonary hypertension can be treated.[56 63] Obviously, the major disadvantages for operating on ECMO are haemostatic.[63 64] Although repairing the diaphragmatic hernia after decannulation from ECMO reduces the risk of haemorrhage, it has a significant disadvantage – namely, the inability to continue ECMO support if recurrent pulmonary hypertension develops. ECMO recannulation may be necessary in these cases. It has been shown, however, that neonates with pulmonary hypertension who are "non-responders" to inhaled NO before placement on ECMO may become "responders" after decannulation from ECMO.[8] It is therefore possible to treat recurrent pulmonary hypertension with inhaled NO following decannulation from ECMO, avoiding a second run of ECMO.[8] Differences in response to inhaled NO before ECMO and following decannulation from ECMO may be due to several factors – for example, time on ECMO, anatomical and functional vascular recovery, and surfactant maturation.[8]

If lung size is not sufficient to support extrauterine life, then ECMO will prolong life but will not affect the outcome as it does not treat pulmonary hypoplasia.[65] To overcome this dilemma, many centres have developed rigid entry criteria in addition to the gestational age, birth weight, and absence of lethal associated abnormalities. Another important criterion is a blood gas tension that is indicative of sufficient lung parenchyma to allow both oxygenation and ventilation. This is usually defined as a best post-ductal P_{CO_2} exceeding 13.3 kPa (100 mm Hg).[66] These classification schemes need modification as atelectatic lungs are surfactant deficient and best post-ductal blood gas tensions may not be indicative of life threatening lung hypoplasia but of inadequate alveolar recruitment. Optimisation of total lung capacity (TLC) and functional residual capacity (FRC) using combinations of the modalities described here are required before it is determined that lethal hypoplasia exists – "making the most out of the least".

LIQUID VENTILATION

Liquid ventilation has been shown to be effective in premature surfactant deficient animal models of respiratory insufficiency, improving compliance, gas exchange, and survival when compared with conventional mechanical ventilation.[67] PAGE has been used in the lamb model of CDH, both prophylactically and as rescue therapy.[49 50 68] In PAGE the lungs are filled with perfluorocarbon to a physiological FRC. By maintaining FRC, altered surface tension induced alveolar collapse is reduced. Perfluorocarbons have a surface tension of approximately 19 dynes/cm, which allows them to serve as excellent substitutes for surfactant.[68] A low surface tension environment is produced which allows for optimal alveolar recruitment and effective gas exchange during ventilation. These properties enable PAGE to be clinically useful when the surfactant system is abnormal. Our preliminary results have shown that PAGE significantly improves gas exchange, dynamic compliance, and tidal volumes when used either prophylactically or as rescue therapy.[49 50] It has also been shown that inhaled NO can be delivered during PAGE to reduce pulmonary pressures and further enhance oxygenation.[49 50] Further studies are necessary to improve our understanding of PAGE and to assess its impact on pulmonary blood flow and haemodynamics.[49 50] Clinical trials for the treatment of CDH will be initiated in the near future.

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